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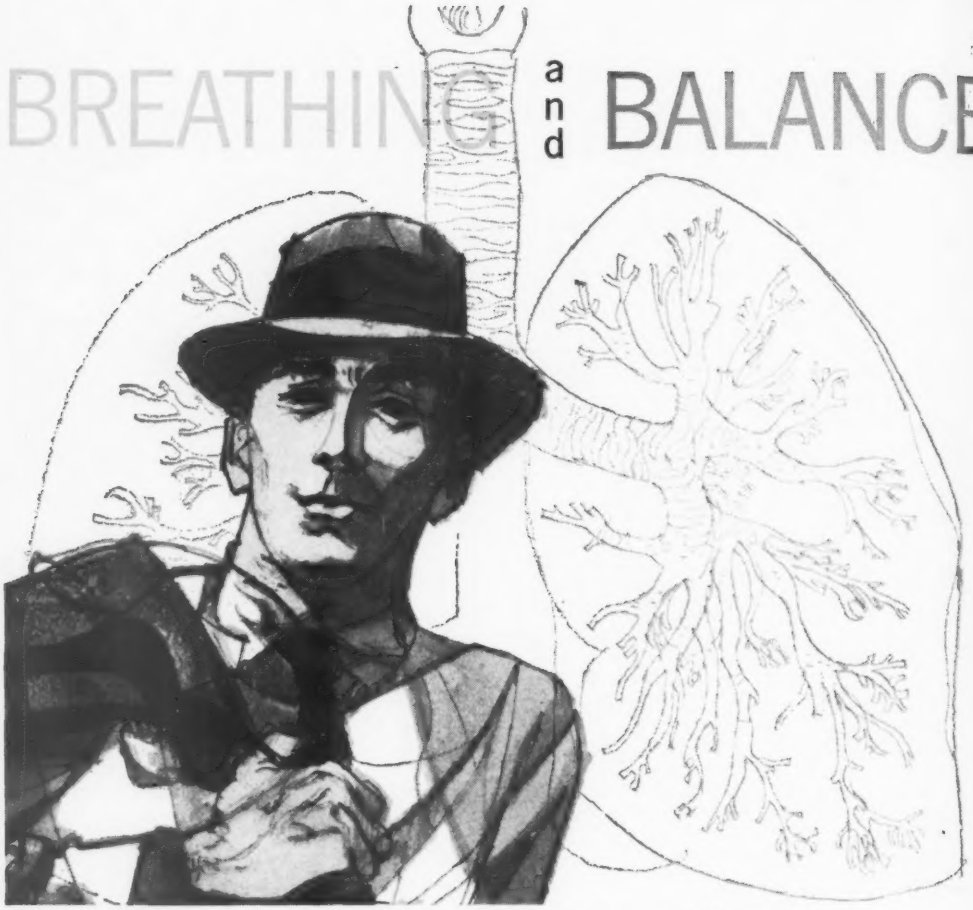

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1957

ORIGINAL ARTICLES

URINARY OSMOLAR CONCENTRATION IN THE HYDROPENIC STATE AS A MEASURE OF RENAL TUBULAR FUNCTION: A TEST FOR EARLY RENAL IMPAIRMENT: PRELIMINARY REPORT*

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The ability of the kidneys to concentrate or dilute urine, as measured by specific gravity, has long been utilized as a method of testing renal tubular function. Final urinary composition is a mixture of both electrolytes and non-electrolytes. Hence, the specific gravity, or density (the ratio of the weight of the urine to the weight of an equal volume of water) is at best a rough estimate of the final urinary concentration. By present standards, the specific gravity is not an accurate or even direct measurement of tubular work, being affected significantly by temperature, pH, and various solutes such as urea, creatinine, sugar and protein. On the other hand, the total solute concentration is a more accurate indication of the tubular concentrating mechanism and is an absolute measure of the number of dissolved particles in solution; and hence correctly estimates the contribution of the ionized electrolytes as well as the effect of the non-electrolytes. Comparison of urinary specific gravity and actual osmolar concentration of the urine has been pre-

*This work was aided by a grant of the Foundation for Cardiovascular Research and the National Institutes of Health (Grant H141) and Eli Lilly and Company, Indianapolis, Indiana.

viously investigated in normal patients (Rapoport *et al.*[7]), in patients with renal disease (Frank, Dreifus and Bellet[5], Hopper, Bolomey and Wenneslland[6], and Rapoport *et al.*[7]), and in patients with diabetes insipidus (Dreifus, Frank and Bellet[8]) and in patients with sickle cell anemia (Zarafonetis *et al.*[12]). These studies have shown that there is no linear relationship between specific gravity and osmolar concentration of the urine.

The purpose of the present study was to correlate the commonly used renal functions tests (BUN, Fishberg concentration test, and PSP test) with the maximal tubular concentration function as determined by osmotic pressure of the urine under hydropenic conditions. This latter measure of renal function gives an accurate quantitative value of solute concentration which we have found useful in evaluation and prognosis of the patient with renal disease. In addition, we have found it to be a useful baseline measurement for future comparison in the management of these patients. We have previously utilized this principle in evaluating the renal function in patients with congestive heart failure[5].

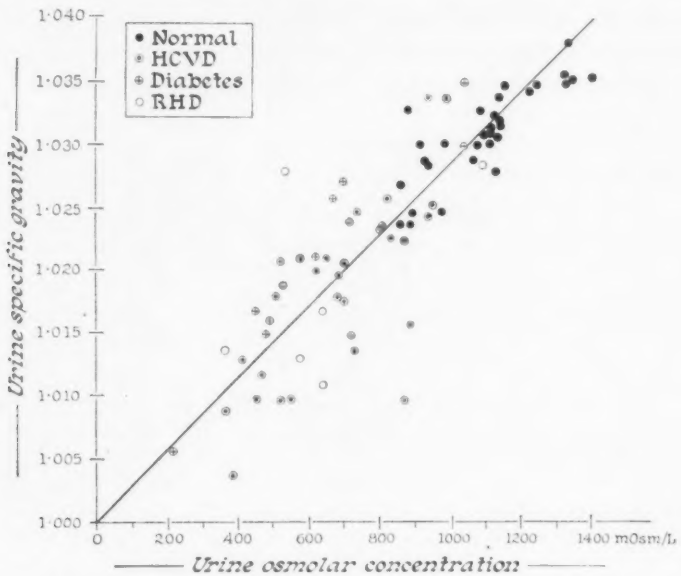

Fig. 1.—The relationship between urinary specific gravity and urinary osmolar concentration in the normal and disease states. The ordinate represents urinary specific gravity. The abscissa represents urine osmolar concentration in mOsm./L.

Methods and Materials. A total of 74 patients, including 32 normal subjects, 27 patients with essential hypertension, 13 with diabetes mellitus, and 7 with compensated rheumatic heart disease were selected for this study from the Medical Wards and Hypertension Clinic of the Philadelphia General Hospital. In the latter three groups, a diagnosis of renal disease could not be substantiated from the ordinary renal studies of blood urea nitrogen, or urinalysis. A group of terminal uremic subjects, which is to be the subject of a separate communication, was also evaluated.

The blood urea nitrogen, specific gravity and total solute concentration of the urine were performed on all patients. PSP tests were performed on the majority of the patients in

the hypertensive and diabetes mellitus groups. The patients were maintained on a regular hospital diet, except where a 2-gm. sodium chloride diet was substituted in a few patients with previous congestive heart failure.

The test of urinary osmolar concentration was performed in a manner similar to the standard Fishberg concentration test. The subjects had a dry supper, and all food and water was withheld from 6 p.m. to 8 a.m. The bladder was emptied at 8 a.m. and a 2-hour specimen of urine was collected. The specific gravity was carefully determined with an ordinary hydrometer. The total solute concentration of the urine was determined by the method of depression of the freezing point using the Fiske apparatus.

Results. There was fairly good linear correlation of urinary specific gravity and urinary osmolar concentration in the hydropenic state in normal patients (Fig. 1). However, patients with essential hypertension, diabetes mellitus, and rheumatic heart disease showed a lack of correlation between these two measurements (Fig. 1). Some patients with apparently fixed urinary specific gravity values of 1.009 to 1.015 exhibited fairly high urinary total solute concentrations of 600 to 800 mOsm./L. Conversely, urinary specific gravity values in the range of 1.020 were sometimes present when urinary osmolar concentration was 400 to 500 mOsm./L.

Urinary osmolar concentrations of 800 mOsm./L. or above were present in all normal control patients (878 mOsm./L. to 1484 mOsm./L.). On the other hand, urinary osmolar concentrations of 400 mOsm./L. or less were found in patients with renal failure, azotemia, hyperphosphatemia, and deranged blood electrolytes. A uremic demise almost inevitably followed in this latter group of patients[11]. A useful gradation of renal tubular function can be estimated from the total solute concentrations of the urine (Table 1).

TABLE 1.—DISTRIBUTION OF OSMOLAR URINARY CONCENTRATION IN VARIOUS DISEASE STATES

mOsm./L.	*Hypertensive Vascular Disease*	*Diabetes Mellitus*	*Rheumatic Heart Disease*	*Normal*
800 or greater, excellent	9	2	1	32
600 to 800, good	8	6	2	—
400 to 600, fair	8	4	3	—
400 or less, poor	2	1	1	—
TOTAL	27	13	7	32

Both the hypertensive and diabetic patients exhibited an early inability maximally to concentrate urinary solutes. This tubular defect was often evident before routine clinical urinary function studies suggested renal impairment (Table 2).

TABLE 2.—COMPARISON OF THE URINARY SPECIFIC GRAVITY TO THE URINARY OSMOLAR CONCENTRATIONS

		Specific Gravity	*Total Solute Concentration mOsm./L.*
Normals	Mean	1.031	1076.0
	S.D.	±.0039	±167.4
	S.E.	±.0022	±96.8
Hypertension	Mean	1.017	643.
	S.D.	±.0071	±180.0
	S.E.	±.0041	±104.0
Diabetes Mellitus	Mean	1.021	648.
	S.D.	±.0076	±232.1
	S.E.	±.0044	±134.2
Rheumatic Heart Disease	Mean	1.019	611.
		±.0079	±225.1
		±.0046	±130.1

S.D. Standard deviation.
S.E. Standard error.

Discussion. We are in agreement with others (Baldwin *et al.*[1] and

Smith[9]) that the urinary specific gravity is only a rough estimation of renal tubular concentrating ability. Furthermore, the correlation of specific gravity and total solute concentration in disease states indicates that various urinary constituents such as urea, creatinine, protein and sugar do not affect the specific gravity to the same degree as electrolytes, particularly when abnormal amounts of these nonelectrolyte solutes are excreted.

The results of this study suggest that osmolar concentration of the urine may offer a relatively simple measurement of early loss of renal tubular concentrating ability. It should be pointed out that the maximum osmolar concentration of the urine is a measure of "potential" energy of the renal tubular mechanism of urinary concentration. Baldwin, Berman, Heinemann and Smith[1] suggest that the basic physiological mechanism of tubular function can be judged only in terms of the free water clearance. This is designated as $T^c_m\ H_2O$ and relates the amount of solute-free water that is removed by the tubules in concentrating the urine under conditions of maximal diuresis. The osmotic work engendered by a solute diuresis such as mannitol or saline loading would then represent the maximal "kinetic" tubular work (Rapoport, Brodsky and West[8]). The flow-load relationship manifests the concentrating ability of the renal tubules under maximal activity. It is possible that the high urinary osmotic concentrations and low urine flows during hydropenia would require a greater activity of the concentrating mechanisms than the flow-load relationship that is achieved during osmotic diuresis. Baldwin *et al.*[1] logically doubt that two separate and distinct mechanisms would exist for the reabsorption of solute-free water, one mechanism operating in the oliguric state, and the other during the diuretic state of the kidney. It is probable that the maximal U/P* solute ratio represents the limiting ratio of urinary osmolar concentration to plasma osmolar concentration gradient across the renal tubules; that is, the maximal concentrating ability of the tubules. We found that the plasma solute concentration measurement did not significantly alter our results since the plasma solute concentration is relatively stable; hence it was decided for the sake of simplicity to measure urinary osmolar concentration only.

During osmotic diuresis, when the U/P solute ratio approaches one, and in instances of severe renal impairment when a hypotonic urine may be excreted in the face of hydropenia (U/P solute ratio less than one), the solute-free water ($T^c_{H_2O}$) would be a negative value, and thus meaningless. If a function test is required under these circumstances, it would be mandatory to measure renal tubular function in the hydropenic state.

In our hypertensive and diabetic groups of patients without clinical or laboratory evidence of renal dysfunction the urinary osmolar concentration often indicated impairment of renal tubular function. It would appear that urinary osmolar concentration could serve as a quantitative index for the evaluation of the renal status before and after the institution of various types of therapy. The simplicity of a single quantitative test, indicating renal impairment early and prior to alterations in the existing renal function tests, may be a valuable aid in the diagnosis, course and prognosis of the patient with suspected renal disease.

Summary and Conclusions. 1. The maximum urinary concentration during the hydropenic state has been examined in 32 normal patients, 27 patients with

*Ratio of urinary osmolar concentration to plasma osmolar concentration.

essential hypertension, 13 patients with diabetes mellitus and 7 patients with compensated rheumatic heart disease.

2. The lack of correlation of urinary specific gravity and the urinary osmolar concentration is attributed to the fact that solutes, protein, sugar, temperature, pH, and the like, contribute differently to the specific gravity and to the osmotic pressure.

3. Patients capable of elaborating urinary concentrations of 800 mOsm./L. or more were considered to have adequate renal function. Those in the range of 600 to 800 mOsm./L. were considered to have good function, 400 to 600 mOsm./L., fair and 400 mOsm./L. or less, were considered to have severe renal disease.

4. This test may serve as a graded quantitative method of evaluating tubular function, and following the course of renal disease, especially in those patients with minimal tubular impairment.

5. There was decrease in concentrating function, as measured by this method, in patients with essential hypertension and diabetes mellitus prior to alteration of other commonly used urinary function tests or a clinical suspicion of renal disease.

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(Interlingua on page 152)

LOW HEMOGLOBIN LEVELS IN MEN

By George W. Hervey, Sc.D.

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Presumably those men who volunteer to give blood for medical use feel physically able. In the course of a period of 2 or 3 weeks, urban persons within the permissible age range, 18 through 59 years, present themselves in adequate numbers and from sufficiently diverse social and economic backgrounds to represent satisfactorily the larger, circumscribed population stratum whence male donor panels come. They do not typify the corresponding general male population since the latter embraces not only seemingly healthy men but also the hospitalized, the ill but not hospitalized, and others who for physical or medical reasons would refrain from coming to donate at blood collecting centers or mobile unit operations. This distinction should always be remembered when contemplating the fact that, even though the men who respond may be considered above average from the standpoint of apparent health, low hemoglobin levels cause numerous individuals to be disqualified by the physicians in charge.

We can now report the findings from data pertaining to 4,993 men, recorded in Los Angeles on 14 days during the period July 8 to 25, 1955. Designedly the sample included no individual who had ever been turned down for any medical reasons. In the foregoing period, 8.17% failed to meet a minimum requirement of 13.5 gm. of hemoglobin per 100 ml. of blood, tested with copper sulfate solution at specific gravity 1.055. To consider possible bases for evaluating the disqualifications we have concentrated on three factors: (1) the number of past donations by an individual; (2) elapsed interval (months) between last donation and return to make a new one; and (3) his age.

In the Los Angeles material indications of a progressive "survival of the fittest" lend substance to an intimation by Bryce and Jacobowicz[1] that the percentage due to low hemoglobin levels may be affected by unconscious selection by blood donors themselves, especially older persons. Table 1 shows that, in general, the more numerous the past donations (1) the less numerous were the men who volunteered to give blood during the period considered; (2) the relatively fewer were the disqualifications; and (3) the older the men. The types of relations reported here in connection with past donations, which may be unique to Los Angeles in some respects, do not run contrary to the more general age considerations discussed subsequently.

On the subject of the optimum interval between donations, the sample size allows scope for dealing in a statistically

*Dr. Adashek is Medical Director of the Los Angeles (Red Cross) Regional Blood Program.

significant way with only broad classes (Table 2). It is possible to say that the men who had previously given blood qualified in larger percentage than those registering for the first time; also that the men, who subsequent to donating waited at least 4 months before volunteering again, qualified in larger percentage than those returning sooner.* Since the figures depict a inquiry reveals a similar difference in other regions. In regard to the more numerous rejections among first-timers as compared to repeaters, some ground exists for believing that the phenomenon holds on a wide front and that the difference varies in magnitude geographically for a specified period and seasonally for a specified region.† None of these remarks should be interpreted

TABLE 1.—NUMBER OF MEN ACCEPTED AND NUMBER DISQUALIFIED BECAUSE OF LOW HEMOGLOBIN LEVELS, WITH RELATED DATA, SHOWN ACCORDING TO PAST DONATIONS

Past donations (Number)	*Number of men*			*Disqualification percentage*	*Average months since last donation, for men*		*Average age (years) of men*	
	Accepted	*Disqualified*	*Both classes*		*Accepted*	*Disqualified*	*Accepted*	*Disqualified*
0	1,837	181	2,018	8.97	0	0	32.3	35.2
1	752	74	826	8.96	17.4	16.4	34.4	35.4
0, 1	2,589	255	2,844	8.97	5.1	4.8	32.9	35.2
2 or more	1,996	153	2,149	7.12	10.8	9.6	37.4	40.7
0, 1, 2	3,103	294	3,397	8.65	6.8	5.7	33.5	35.8
3 or more	1,482	114	1,596	7.14	9.2	8.9	37.8	41.0
Aggregate[1]	4,585	408	4,993	8.17	[2]7.6	6.6	34.9	37.3

[1] Past donations numbered from 0 to 33. Average excluding 0 class: men accepted, 4.1; men disqualified, 3.9.

[2] Average months excluding 0 class: men accepted 12.6; men disqualified, 11.8.

true operational situation the additional 1.59 persons per 100 that qualified after delaying the interval to 4 or more months cannot be dismissed as inconsequential.

In Los Angeles the effort and cost entailed in recruiting the extra persons needed to overcome the disqualifications for low hemoglobin association with the shorter interval definitely enter into operational planning; and this comment will gain stature if future as necessarily implying a direct cause and effect relationship between blood-donation interval and the incidence of a low hemoglobin level; this question remains open for further study. Not so well indicated as related to the number of past donations, selectivity may offer at least a partial explanation.

Ability of the reticulo-endothelial cells to manufacture hemoglobin in bone marrow is governed by the available quantity of iron and indirectly by

*Of 332 men who returned to give blood between 3 and 4 months of their last preceding donations (Table 2), nearly all did so in the 13th week. The Biologics Act of the State of California has set 12 weeks as the prescribed minimum interval.

†A Los Angeles report for January, 1956, on a sample of 14,304 men shows low hemoglobin levels of 4% for first-timers and 3.78% for repeaters. First-timers numbered 6,628.

Reports for the same month from Portland, Ore.; St. Paul, Minn.; Philadelphia, Pa.; and Charlotte, N.C., on samples extending from 2,690 to 7,794 men showed with one exception (Portland) the disqualifications for first-timers exceeding those for repeaters. Among these regions the over-all rejection percentage varied from 2.34 to 4.97.

a person's health, diet, occupation, perhaps his genetic constitution, and unquestionably his age. That hemoglobin values fall with age has been repeatedly shown. For example, Hawkins, Speck, and Leonard[4] found the values typically to be 14.5 to 15.0 gm. per 100 ml. of blood in men 20 to 60 years, with the average declining to 12.4 gm. at 80 to 90 years. Most frequently stated, hemoglobin decreases after birth, rises at puberty, remains fairly constant until old age, and then falls again (Haden[3] and Rowntree, Brown and Roth[5]). The Los Angeles data (Table 3) now appear to reflect a persistent influence that causes diminution throughout the age range represented.

Persisting against the aforesaid selectivity, the disqualification percentages move irregularly upward along a readily defined curve.* Following a sharp rise for the men from 18 to 30 years, the trend still proceeds upward but with decreased acceleration. At 59 years the relative number of disqualifications is approximately triple the number at 18 years. Pending further study, the variation shown for Los Angeles blood donors in July can be viewed as illustrating the typical character of the gross relation of the disqualifications to age.

Interest grows in the possibility of a connection between hemoglobin values and the environment. Wadsworth[6], for instance, reports that an observed de-

TABLE 2.—MEN ACCEPTED AND THOSE DISQUALIFIED BECAUSE OF LOW HEMOGLOBIN, LEVELS WITH RELATED DATA, SHOWN ACCORDING TO MONTHS SINCE LAST DONATION

Months since last donation	*Number of men*			*Disqualification percentage*	*Average number of past donations by men*		*Average age (years) of men*	
	Accepted	*Disqualified*	*Both classes*		*Accepted*	*Disqualified*	*Accepted*	*Disqualified*
0	1,837	181	2,018	8.97	0	0	32.3	35.2
3–3.9	302	30	332	9.04	6.9	6.1	37.7	39.4
4 or more	2,446	197	2,643	7.45	3.7	3.5	36.5	38.9
Aggregate	4,585	408	4,993	8.17	2.4	2.2	34.9	37.3

TABLE 3.—MEN ACCEPTED AND THOSE DISQUALIFIED BECAUSE OF LOW HEMOGLOBIN LEVELS SHOWN BY AGE CLASSES

Age class (years)	*Average age (years)*	*Number*			*Percentage disqualified*
		Accepted	*Disqualified*	*Total*	
Under 20	18.6	124	5	129	3.88
20–24	22.2	587	46	633	7.27
25–29	27.0	772	51	823	6.20
30–34	32.0	907	68	975	6.97
35–39	36.9	784	68	852	7.98
40–44	42.0	600	69	669	10.31
45–49	46.8	421	52	473	10.99
50–54	51.9	252	33	285	11.58
55–59	56.7	138	16	154	10.39
All classes	35.1	4,585	408	4,993	8.17

*Disqualification percentage $= -15.323 + 15.371 \log_{10}$ Age. In reference to the last column of Table 3: root mean square error, .96.

cline in men who stayed in hot rooms for several days was a temporary condition. Data made available to the authors by Douglass[2], covering 49 Connecticut mobile unit operations conducted over a 32-week period from January 14 to August 20, 1954, disclose a very pronounced upward trend in the disqualifications; and, in addition, we have found a simultaneous, independent upward trend in the official weekly humidity figures for the state. Our review of the Douglass* material stresses the need for caution against ascribing the direct effect of a specific cause to an environmental factor that may be merely coincidental. Thus, changes in nutritional habits with the approach of summer could have much to do with the increased rejections for a low hemoglobin level. The same comment applies to the seasonal differences noted in Los Angeles as stated earlier. We have not found a significant relationship between low hemoglobin rejections and weather conditions during the 14 days in which the Los Angeles data were recorded.

Persons familiar with the technical side of blood program operations will nevertheless agree that various environmental factors inside the collection centers can affect the comparability of the hemoglobin determinations from hour to hour, day to day, or place to place. Is the specific gravity of the copper sulfate solution exactly as stated on the bottle? How long is the solution exposed to air between times of use? From one donor to the next, is the blood dropped into the solution from a constant height? Is the donor's finger absolutely dry? Is the finger puncture adequate to assure a free flow of blood? In the Los Angeles study the determinations were made with full realization of the importance of these points, and uniformity was maintained so far as practicable.

Summary. Data pertaining to 4,993 men in the age range 18 through 59 years who volunteered to give blood in Los Angeles on 14 days in July, 1955, disclose that low hemoglobin levels caused 8.17% to be disqualified. This compares with approximately 4% for a sample of 14,304 men reported for January, 1956, indicating a strong seasonal variation. The July data reviewed in detail, appear to signify that, mainly as the result of self-screening by many Los Angeles individuals, the more numerous the past donations the relatively fewer were the rejections. Persisting against such selectivity, however, the disqualification percentages in general tended to be higher for the older men. Individuals, who, having previously given blood, waited at least 4 months before donating were rejected less numerously than those returning under 4 months. The authors caution against placing cause-and-effect interpretations on the relationships yielded by such mass data, and stress the need of further study to establish possible connections between numerous environmental factors and the incidence of low hemoglobin levels.

*Dr. Wallace C. Douglass, Cos Cob, Connecticut, is a member of the medical staff of the Connecticut (Red Cross) Regional Blood Program and an active student of climatology in relation to low hemoglobin levels.

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SUMMARIO IN INTERLINGUA

Basse Nivellos de Hemoglobina in Masculos

Datos in re 4.993 masculos de etates de inter 18 e 59 annos, qui se presentava a Los Angeles a un de 14 dies de julio 1955 como donatores voluntari de sanguine, revela que basse nivellos de hemoglobina esseva le causa disqualificatori in 8,17% del casos. Le juxtaposition de iste facto con le correspondente valor de circa 4% que esseva reportate in januario 1956 pro un gruppo de 14.304 masculos indica un forte variation saisonal. Le revista detaliate del datos obtenite in julio pare indicar que le voluntarios a Los Angeles practica un specie de auto-selection que resulta in un correlation inverse inter le numero del donationes passate e le probabilitate del rejection. Tamen, sin relation a iste principio de selection, le procentage de disqualification tendeva in general a montar inter masculos de etate plus avantiate. Re-donatores qui habeva attendite 4 menses o plus ante que illes se presentava de novo esseva rejicite in minus grande numeros que illes qui retornava in minus que 4 menses. Le autores consilia contra le stipulation de un relation de causa e effecto inter le constatationes derivate ab tal datos in massa. Illes sublinea le necessitate de studios additional pro establir connexiones possibile inter varie factores ambiental e le incidentia de basse nivellos de hemoglobina.

CHLORPROMAZINE THERAPY IN CHILDREN AT THE FLORIDA FARM COLONY

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and

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Although the effects of chlorpromazine in adult neuropsychiatric patients have been widely reported during the last 2 years, attention was not at first given to the use of the drug in children. More recently, results in small series of children have been reported, but no studies of large series have appeared in the literature. Administration of the drug to children has been approached cautiously, as its effects upon the adult organism have become more fully known. Winkelman[11] and Moyer, Kinross-Wright, and Finney[9] were among the first to report on the drug in psychoneurotics and psychotics. Other investigators (Goldman[7], Lehmann and Hanrahan[8], and Pollack[10]) have found chlorpromazine effective in many psychotic conditions marked by anxiety or agitation, and in psychoneuroses, as well. Freed and Peifer[6] noted a general lessening of overactivity in hyperkinetic, emotionally disturbed children. Bair and Herold[1] reported a significant rise in I.Q. and improved response to psychotherapy in hyperactive, mentally retarded children. Flaherty[5] found that children receiving chlorpromazine experienced diminished aggressiveness and hostility and were more approachable.

At the Florida Farm Colony we undertook to evaluate chlorpromazine in a large series of children, hoping to achieve results comparable with those reported in large series of adults. Previous experience with chemotherapeutic agents had convinced us that excessive sedation is unproductive in itself and renders patients inaccessible to psychotherapy and sociotherapy. Our problem, unlike that of the clinician treating adults, was not one of simply restoring the patient to a former, already developed state, but was one of helping the child to achieve a state in which further development would be possible through schooling and training. In some cases, we hoped to arrest psychotic or neurotic processes; in other cases we faced a coexisting somatic condition that hampered or virtually prevented progress toward normal adult development.

Materials and Methods. We classified the 153 children in this series in four broad groups: mental defectives, pre-psychotics, epileptics, and spastics. The first two groups included many cases which we were able to classify according to a specific disorder, but also many cases which were borderline or presented a variety of symptoms which made definite classification infeasible, although we were able to determine therapy on the basis of dominant symptoms.

All of the patients were treated with chlorpromazine for at least 6 months, and most for 9 months. Some were treated for a year or longer. Although individual daily dosages ranged between 30 mg. and 600 mg., most patients received 75 mg. or 150 mg. In some cases, 5 mg. to 10 mg. of dextro-amphetamine sulfate were added to the daily regimen.

Our series included 52 pre-psychotics. This group consisted of 5 paranoid types, 5 catatonic schizophrenic types, 10 manic de-

pressive types, 27 neurotics, one psychoneurotic, 2 children with migraine, and 2 suffering confused states, with epilepsy as a complication. Familiar manifestations of these conditions included temper outbursts, fights, constant complaints of aches and pains without physiological basis, continual requests for medication, violent dreams and crying out, complete withdrawal, anorexia, and insomnia.

We treated 57 mental defectives, of whom 9 had suffered brain injuries, one was mongoloid, and 10 were low grade morons. Relying chiefly on major symptoms in classifying these children, we considered 30 of them hyperactive (assaultive and destructive); 2, self-destructive; 6, hyperirritable; and 13, schizophrenic. Among the schizophrenics three were chronic regurgitators and three were chronic masturbators. The abnormal activities and psychic patterns we observed in the pre-psychotics were exaggerated in the mental defectives. Electroencephalograms revealed excessive gamma wave activity in these patients. We noted more purposeless motion or constant walking, pulling hair and biting of other patients, continual nose-picking, and such unusual activities as rubbing or hitting the head on the floor to remove hair or induce bleeding.

Of the 28 epileptics, (not including the 2 pre-psychotics mentioned above) we treated most for 6 months, a few for 9 months. Bonafede[3] had reported the efficacy of chlorpromazine in epileptics. Our chief interest in these children was to determine the efficacy of the drug in relieving pre- and post-seizure tension and the anxiety caused by indications of an approaching seizure. Where these emotional factors could be diminished or relieved, we hoped to find improvement in the patient's general adjustment to his condition and to institutional routine.

In the 16 spastics we determined to evaluate the effect of chlorpromazine on muscular relaxation and coordination, as well as in improving the attitude toward physical therapy. We added mephenesin and glutamic acid to the regimens of some spastics.

Among the pre-psychotics we hoped for complete relief of symptoms and normal progress in school and training in those cases responding fully to chlorpromazine. However, we realized originally that our expression of results in mental defectives would have to be qualified. These children were classified in this group because of organic deficiency or brain injury; we considered them lacking in basic capacity for normal development. We could not expect them to progress at the rate of the pre-psychotics. Significant improvements in their conditions and their adjustments to daily routine seemed to us reasonable expectations, as did response (where it had been lacking) or increased response to the special schooling or training designed for them. In designating results in defectives as "Excellent," we have these qualifications in mind.

Results. In analyzing our results we established the following classifications: "Excellent," full relief of symptoms and full response to training; "Good," relief of major symptoms and improvement in training; "Fair," persistence of some symptoms and limited response to training; and "Poor," persistence of some major symptoms and minimal response to training.

In the series of 153 patients we rated 80 responses (52%) as Excellent, 39 (25%) as Good, 18 (12%) as Fair, and 16 (10%) as Poor. Table 1 presents our results in detail. As indicated above, we did not feel from the start that we could expect the mental defectives to respond as the pre-psychotics did. Neither did we expect complete relief of the basic conditions in epileptics and spastics. The results were nonetheless surprising in certain respects.

In the pre-psychotic group we rated 28 responses as Excellent, 19 as Good, 3 as Fair, and 2 as Poor. The best results were achieved among manic types, neurotics, and the 2 children with migraine. Chlorpromazine alone appeared less effective in manic and catatonic schizophrenic types, but many of these patients improved significantly after the addition of dextro-amphetamine sulfate to their regimens. Behavior problems, normally most numerous among the pre-psychotics, have been all but eliminated since we began therapy with chlorpromazine. The drug was effective in many of these patients within a day or two; in most, within a week; in nearly all, within the first month.

Results in the mental defective group were better and more extensive than

we had anticipated. We considered the results Excellent in 39 patients, Good in 8, Fair in 8, and Poor in 2. Electroencephalograms made after the start of chlorpromazine therapy showed that much of the excessive gamma wave activity had disappeared. These patients became much quieter and lost their anxious expressions. The drug was very effective in hyperactive and hyperirritable patients and in the schizophrenics. It gave full symptomatic relief in the self-destructive and masturbatory patients and considerable relief in the regurgitators. Furthermore, bizarre and violent activities were virtually eliminated; the usual aberrations of constant motion, frightening dreams, and frequent psychosomatic complaints were greatly reduced; and many patients showed considerable progress in training and schooling, where before these patients had shown little or no response. Most of the defectives responded to the drug within 2 weeks, and practically all within 4 weeks, although a few responded after 8 weeks.

In the epileptic group we graded the results Excellent in 10, Good in 5, Fair in one, and Poor in 12. Although statistically less impressive than in the other groups, the results in these patients were encouraging in a number of other respects. Chlorpromazine reduced pre- and post-seizure tension and the dread of approaching seizures. In the epileptics receiving the drug there was very little indication of approaching seizures. We also noted some reduction in the number and severity of seizures. Although we were not able to reduce anti-convulsive medication in most of the patients on chlorpromazine, we did not have to increase the medication in any case. Hostility and excitement generally decreased among these patients during the course of therapy.

In the spastics the drug produced 3 Excellent, 7 Good and 6 Fair results. It had, then, an appreciable effect in all of these patients. It produced a good degree of muscular relaxation and increase in muscular coordination. Although these patients seemed previously afraid to try to walk, three of them have made sustained efforts since being given chlorpromazine. Five of them have begun to say words since the medication was started. In all of the spastics, hyperirritability

TABLE 1.—RESULTS OF THERAPY WITH CHLORPROMAZINE

Condition	*No. of Pts.*	*Results*			
		Excellent	*Good*	*Fair*	*Poor*
Mental Defectives:	57	39	8	8	2
Hyperactive	27	19	2	4	2
Self-destructive	2	2	–	–	–
Schizophrenic	13	9	3	1	–
Hyperirritable	12	8	3	1	–
Borderline Pre-Psychotics:	52	28	19	3	2
Catatonic Schizophrenic type	5	0	2	2	1
Manic type	10	8	2	–	–
Neurotic	27	17	9	1	–
Migraine	2	2	–	–	–
Paranoid type	5	1	3	–	1
Psychoneurotic	1	–	1	–	–
Confused state (with epilepsy)	2	–	2	–	–
Epileptics:	28	10	5	1	12
Spastics:	16	3	7	6	0
Totals	153	80	39	18	16

has been decreased. This benefit was particularly apparent in the patients receiving a combination of chlorpromazine and mephenesin, and to a lesser extent in those receiving a combination of chlorpromazine and glutamic acid. Either combination appeared to produce better relaxation of the skeletal muscles than chlorpromazine alone or than the muscle relaxants alone.

Results observed generally among the 153 patients included a tendency for body weights to return to normal in those patients who had been overweight or underweight prior to the start of therapy. Sleep patterns were considerably improved, and the cumulative effect of this in the full group measurably improved the atmosphere of the wards. The general conduct of the patients has so improved that we have virtually done away with punishments.

The only side effect we encountered in this series was mild drowsiness, in patients receiving relatively high dosages. Other observers have reported other undesirable actions, including jaundice of an obstructive nature in approximately 0.1% of cases (Doughty[4]) and agranulocytosis in rare instances (Boleman[2]).

Discussion. In agitated, excited patients, whether mentally defective or mentally ill, we have found chlorpromazine highly effective. We feel that chlorpromazine has a wider range of applications than any chemotherapeutic agent in general use in such patients.

Most of the pre-psychotics have benefited sufficiently from the drug to proceed with normal training and schooling to the full, or to a very large, extent. Symptoms of the basic psychotic or neurotic processes have been relieved. Temper outbursts, fights, complaints of aches and pains, requests for medication, and nightmares have been almost eliminated. Flaherty[5] has reported that children treated with chlorpromazine acknowledged the decrease of hostile feelings and the increase of approachability. We feel that our patients are aware of the improvements in themselves; they are happier and normally interested in their surroundings and their place in the daily routine.

Various manifestations of possible frustrations: the crying spells, screaming, and anxious expressions, have begun to clear up in practically every mental defective treated. Patients in this group have not only been relieved of symptoms troublesome to others and themselves, but also have been able to improve themselves in varying degrees. Though the improvements in response to training do not constitute normal development, many of these children have come to know some sense of accomplishment, however minor. They have been released from the continual care and surveillance of virtual helplessness. Their constant, purposeless activities and animal assaultiveness have been greatly reduced. Though it seems improbable that more than a few in this group will ever approach normal development, many of them have been relieved of anxieties and agitations which had beset them. For the first time since they have been admitted to the institution they respond to the ward life about them and enjoy greater comfort.

Defectives and pre-psychotics ordinarily present problems which greatly increase the work load and the psychological strain of our entire staff. The biting and scratching of other patients, crying out, breaking windows, and tearing of clothes, bed linen and towels frequently disturb the atmosphere of the entire institution. In addition to the special consideration they require, the epileptics and spastics present many of the same problems. Widespread violence or confusion may be touched off by in-

dividual patients or small groups. Such outbreaks often nullify the work of days or weeks of training or psychotherapy. They also multiply individual problems of insomnia or refusal to eat or to participate in planned activity.

Since we began administering chlorpromazine, the hostility and destruction have been reduced to occasional outbursts by a few patients. The generalized confusion and disruption of routine have been eliminated. The repulsive symptoms, found especially among the regurgitators, have been almost completely relieved. The atmosphere is now conducive to the individual patient's progress, and our staff is much better able to carry out our programs.

The periodic interference with consciousness in epileptics and the constant interference in spastics complicated efforts at therapy for these patients. Here adjustment to routine is difficult, and progress can be made only against frequent interruption. Decrease in tension usually improves rapport between patient and staff. This improved rapport is sometimes the opening wedge of progress in ward routine and schooling. Both the epileptics and the spastics are much more cooperative and seem much happier since they have been on chlorpromazine.

Summary and Conclusions. 1. Chlorpromazine was administered for a period of 6 to 8 months to 153 mentally defective, pre-psychotic, epileptic, or spastic children at the Florida Farm Colony.

2. Daily dosages ranged between 30 mg. and 600 mg., with most patients receiving 75 mg. or 150 mg.

3. Results were rated Excellent in 80 cases (52%), Good in 39 (25%), Fair in 18 (12%), and Poor in 16 (10%).

4. Hostility, hypochondria, fear, and withdrawal were greatly reduced or eliminated in individual patients, and general disturbances of ward routine by violence or apprehension were eliminated. Destruction of property was reduced.

5. Pre-psychotics and mental defectives were relieved of disturbing symptoms and enabled to respond to training and schooling. Chlorpromazine reduced pre- and post-seizure tension and dread of approaching seizures in epileptics. The drug produced a good degree of muscular relaxation and increase in muscular coordination in spastics. A combination of chlorpromazine and mephenesin, or chlorpromazine and glutamic acid, gave better relaxation of skeletal muscles than did either chlorpromazine or the muscle relaxants alone.

6. The over-all atmosphere of the institution was significantly improved. Conduct of programs was facilitated for the staff.

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SUMMARIO IN INTERLINGUA

Chlorpromazina in le Therapia de Juveniles al Colonia Agricole de Gainesville, Florida

1. Chlorpromazina esseva administrate durante un periodo de 6 a 8 menses a 153 mentalmente defective, pre-psychotic, epileptic, o spastic juveniles al Colonia Agricole de Gainesville, Florida (Florida Farm Colony).

2. Le doses diurne variava inter 30 e 600 mg. Le majoritate del patientes recipeva 75 o 150 mg.

3. Le resultatos esseva classificate como excellente in 80 casos (52%), bon in 39 (25%), satis bon in 18 (12%), e non bon in 16(10%).

4. Hostilitate, hypochondria, timor, e reticentia esseva grandemente reducite o eliminate in patientes individual, e disturbationes del vita routinari del instituto per violentia o apprehension esseva eliminate. Le destruction de installationes esseva reducite.

5. Patientes del gruppos pre-psychotic e mentalmente defective experientiava un alleviation de symptomas disturbante e deveniva capace a responder al instruction e al exercitios. In epilepticos, chlorpromazina reduceva le tension ante e post le attaccos e le horror de attaccos futur. Le droga produceva un bon grado de relaxation muscular e un augmento del coordination muscular in patientes spastic. Un combination de chlorpromazina con mephenesina o de chlorpromazina con acido glutamic produceva un melior grado de relaxation skeletic que le un o le altere sol.

6. Le atmosphera general del institution esseva significativemente meliorate. Le personal trovava plus facile executar lor varie programmas.

COMPARISON OF CLINICAL EFFECTS OF CHLORPROMAZINE* AND RESERPINE† IN PSYCHOTIC PATIENTS

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Chlorpromazine and reserpine, the two most useful and potent phrenotropic drugs, have now had a period of more than 2 years of application in American psychiatric hospitals. It is fortunate that psychiatrists who, in spite of previously inadequate pharmacologic background generally, were charged with the responsibility of developing methods of application of such drugs, did not become divided into opposing groups each advocating the virtues of one compound over another. It has been necessary to mature rapidly in the acquisition of clinical pharmacologic skill and make a dispassionate assessment of the usefulness of each compound in relieving psychotic reactions.

The purpose of this essay is to assess the value of these two compounds in psychiatric practice, not with the purpose of eliminating one or the other, but to determine fields of usefulness and limitations of clinical importance in the light of traditional therapeutic philosophy. Experience indicates similarities and differences as well as areas of coincidence of usefulness between the two drugs, some exclusive indications as well as contraindications for the individual drugs, and some controversial observations requiring further work. What is clearly evident at this time is that any newer compound proposed for treatment of psychotic illness must compare in effectiveness with these drugs to achieve recognition. Earlier reports of comparison of effects of these two drugs have been made by Kinross-Wright[2] and by Bleuler and Stoll[1].

Technique of application. Both chlorpromazine and reserpine can be given parenterally and orally. The oral preparations of the two drugs are equally acceptable to patients in tablets or in suitably prepared solutions. The drugs can both be given by mouth to the level of maximum pharmacologic effect within the therapeutic range and beyond. Reserpine treatment is often initiated with large doses and then decreased, while chlorpromazine is best given in gradually increasing doses. Parenteral preparations of chlorpromazine so far available are limited by the irritating quality of the necessary solvent. By diluting the solution available with equal parts of physiologic saline and the addition of a small amount of hyaluronidase, the maximum amount of chlorpromazine which can be administered is 200 mg. every 6 hours with local irritation limiting therapy after 3 to 6 days. This is often in severely psychotic individuals not the maximum required dose. We have found that by using concentrated solutions of chlorpromazine by gavage rather than the parenteral treatment, larger and more adequate amounts of the drug can be given to patients who are unable or unwilling to swallow medicine. Reserpine solutions available for injection are much less irritating and can be given in amounts comparable

*Chlorpromazine furnished gratis by Smith, Kline & French Laboratories.

†Reserpine furnished gratis by: E. R. Squibb & Sons Co.; Smith, Kline & French Laboratories; Riker Laboratories; and Ciba Pharmaceutical Products, Inc.

in magnitude and effect with the oral preparations. The problem of administering maximal amounts of drug by injection fortunately occurs only in the most acutely psychotic individuals and the most intractable disturbed chronic psychotic patients. In the initial period of treatment of such severely psychotic individuals either drug alone or both drugs together must at times be used at maximum levels for production of adequate effect without regard to side-effects and complications. Such heroic therapy is not to be attempted by the tyro or the timid (Table 1).

Reserpine is in many respects similar to chlorpromazine in the production of somnolence and lethargy and occasional angioneurotic edema, but these reactions are likely to be less frequent and less intense than with chlorpromazine. However, reserpine frequently produces what has been called "turbulence" which is essentially an intensification of psychotic manifestations, particularly the hyperkinetic ones. While such "turbulence" is occasionally encountered with chlorpromazine it is much less frequent and much less intense. Orthostatic hypotension is produced by both drugs about equally, both in intensity and number of patients affected. All of these factors affecting the willingness of patients to take medication are minimized by proper preparation of the patients and families to know what to expect and by the establishment of firm confidence in the physician's own sense of security on the part of patients and families. Fortunately these side-effects are of minor importance and transient in the course of treatment with both drugs (Table 2).

TABLE 1.—DOSAGE AND ADMINISTRATION

	Reserpine	*Chlorpromazine*
Oral dose	0.5 mg. to 10 mg. t. i. d. or q. i. d.	25 mg. to 500 mg. t. i. d. or q. i. d.
Intramuscular	2.5 mg. to 10 mg. t. i. d. or q. i. d.	25 mg. to 200 mg.
Intravenous	2.5 mg. to 10 mg.	Only with maximum caution

TABLE 2.—EARLY REACTIONS TO DRUGS AFFECTING ACCEPTABILITY

	Reserpine	*Chlorpromazine*
Sleepiness	++	+++
Hypotension	+	+
Dermal sensitivity	+	+
"Turbulence"	++	+++
Dreams	+	++

ACCEPTABILITY TO PATIENTS. In the management of large groups of psychotic individuals as well as in the treatment of individual patients in private practice the use of these drugs has presented the problem of therapeutic failure from unwillingness of patients to take the medication. Patients in the initial days of chlorpromazine treatment are often sleepy, lethargic and appear to their families and to uninitiated nurses and attendants to be worse than in their original illness. Some patients have frightening dreams, a few develop dermatologic reactions after only a few days of treatment.

COMPLICATIONS. Major complications resulting from administration of both

chlorpromazine and reserpine must be taken seriously into consideration in determining the further course of therapy. The most common complication of treatment, particularly in chronic psychotic individuals who require large doses of medication, either chlorpromazine or reserpine, is parkinsonism. This occurs somewhat more readily and earlier in the course of treatment with reserpine, but with about the same frequency in the course of prolonged therapy with chlorpromazine. Parkinsonism from chlorpromazine is likely to be characterized by more rigidity and less tremor; that produced by reserpine is characterized by more intense and widespread tremor with less rigidity. Other manifestations of extrapyramidal dysfunction, some quite bizarre, are encountered with both drugs at higher dosage levels. Such manifestations must be treated by modification of dosage and administration of Cogentin which affects the parkinsonism of both chlorpromazine and reserpine origin favorably (Table 3).

The more severe dermatologic manifestations, particularly from chlorpromazine, require active clinical interference by modification of dosage and the use of antihistamine and adrenocorticotrophic hormone. The angioneurotic edemas from reserpine are somewhat less frequent but require similar management. The reaction of dermal photosensitivity is peculiar to chlorpromazine. It has never been found dangerous, and always responds to cessation of exposure and suitable treatment for the burn.

The two most unfortunate complications from the use of chlorpromazine are agranulocytosis and jaundice. In our experience these occur in less than 1% of patients treated. The jaundice is invariably benign and does not preclude continuing treatment or resuming treatment after the jaundice subsides. Agranulocytosis, in otherwise uncomplicated reactions, is usually susceptible to treatment by withdrawal of the drug and intensive use of antibiotics and ACTH. Neither jaundice nor agranulocytosis has been encountered from treatment with reserpine. Reserpine, particularly in older individuals, frequently produces marked bradycardia. This is sufficiently severe to require manipulation of dosage in some individuals. Chlorpromazine usually produces tachycardia if it influences the heart rate at all. Such tachycardia is comparatively insignificant clinically. The activation of peptic ulcer and of bronchial asthma occurs with reserpine treatment but rarely or not at all with chlorpromazine (Segal and Attinger[3]).

TABLE 3. COMPLICATIONS AND SEVERE SIDE-EFFECTS

	Reserpine 571 Patients		*Chlorpromazine 1,777 Patients*	
Skin:				
Eruption	9	1.6%	117	6.6%
Edema	13	2.3%	85	4.8%
Parkinsonism	121	21.2%	495	27.9%
Agranulocytosis	0		6	0.34%
Jaundice	0		9	0.51%
Severe hypotension	8	1.4%	22	1.24%
Depression or anxiety, or both	++		+	
Asthma	++		+	
Activation of peptic ulcer	+		?	

CONTRAINDICATIONS. Absolute con-

traindications to the use of the drugs for treatment of psychotic states must be considered rare. For chlorpromazine, the only absolute contraindication is the previous occurrence of agranulocytosis from the use of this drug. For reserpine, absolute contraindication would be the previous occurrence of severe activation of asthma or peptic ulcer by the drug. In addition there are a number of conditional contraindications which must be made between chlorpromazine and reserpine is undoubtedly the comparison in effectiveness in relieving or ameliorating psychotic symptoms and reactions.

Response of specific psychotic manifestations to chlorpromazine and reserpine shows some differential aspects. Organic delirium whether from alcohol or other toxic agent responds rapidly to administration of relatively small

TABLE 4.—CONTRAINDICATIONS

Reserpine	*Chlorpromazine*
ABSOLUTE	
Severe asthma	Agranulocytosis
Peptic ulcer	
CONDITIONAL	
Cardiac abnormalities, failure	
AV block	
Renal failure	
Hepatic failure	
Severe depression	

TABLE 5.—OVER-ALL RESULTS (ALL DIAGNOSES)

	Reserpine					*Chlorpromazine*				
Time in Hospital	*A**	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
0–2 years	1	15	65	20	101	83	188	241	55	567
2–5 years	3	7	46	11	67	13	91	114	20	238
5–10 years		7	39	17	63	9	59	99	18	185
Over 10 years		12	96	78	186	2	57	219	86	364

All patients treated for at least 3 months are tabulated; many have been treated from 6 to 12 months and some longer. Duration of stay in the State Hospital is used as the index of duration rather than duration of illness.

* In this and subsequent tables grades of recovery are indicated as follows: *A* = complete recovery; *B* = good "social" remission short of complete recovery; *C* = improvement less than "*A*" or "*B*"; *D* = no improvement.

cations which must depend upon the clinician's judgment. These conditional contraindications would involve the use of either or both drugs, particularly in the presence of various cardiac abnormalities, particularly atrial fibrillation and other arrhythmias, decompensation and severe hypotension; pre-existing renal or hepatic failure, diabetes, malignant processes and severe infections (Table 4).

RESULT OF TREATMENT. The most important and significant comparison doses of chlorpromazine. Reserpine may have a quieting effect on motor manifestations in delirium but relatively little effect on sensorium. In excited manic or schizo-affective states both drugs are effective, but reserpine can be given in relatively larger doses parenterally and, therefore, may more quickly produce subsidence of motor manifestations in extremely overactive patients. Relief of recently developed anxiety and delusional material responds to both drugs, but the "turbulence" ac-

companying early phases of treatment with reserpine may interfere with the smooth progress of recovery. More chronic paranoid symptoms are resolved only after prolonged treatment if at all in some patients, and it is in this group that chlorpromazine shows clearly more effectiveness than reserpine. In depressive reactions neither with chlorpromazine and reserpine. These tables include all the patients in the diagnostic categories which are treated with the drugs. The largest group treated is the schizophrenic group. In schizophrenic patients hospitalized for less than 6 months, no clear distinction in effectiveness between the two drugs can be made.

TABLE 6-A.—SCHIZOPHRENIC

	Reserpine					*Chlorpromazine*				
Time in Hospital	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
0–2 years	1	9	38	8	56	59	104	110	18	291
2–5 years	2	4	21	6	33	9	60	58	4	131
5–10 years		3	21	8	32	5	32	62	7	106
Over 10 years		9	60	50	119	1	38	131	58	228

All patients treated for at least 3 months

TABLE 6-B.—MANIC-DEPRESSIVE AND INVOLUTIONAL

	Reserpine					*Chlorpromazine*				
Time in Hospital	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
0–2 years		2	6	4	12	8	26	23	7	64
2–5 years		2	8	1	11	4	10	13	3	30
5–10 years		4	6	1	11	1	11	11	4	27
Over 10 years			13	7	20	1	10	36	8	55

All patients treated for at least 3 months

TABLE 6-C.—MISCELLANEOUS

	Reserpine					*Chlorpromazine*				
Time in Hospital	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
0–2 years		4	21	8	33	16	58	108	30	212
2–5 years	1	1	17	4	23		21	43	13	77
5–10 years		1	11	8	20	3	16	26	7	52
Over 10 years		2	24	21	47		9	52	20	81

All patients treated for at least 3 months

drug is likely to be effective. Reserpine particularly may increase depression and not infrequently seems to activate previously entirely latent depression in patients who have received the drug for hypertensive cardiovascular disease. Chlorpromazine has only rarely had this effect in our experience, and then relatively mildly.

Tables 5 and 6-A, -B and -C present comparisons of results of treatment However, in the large and significant group hospitalized for longer periods, chlorpromazine produces a significantly greater proportion of Grade "A" and "B" results. This is true also in the manic-depressive and involutional psychoses and in the "miscellaneous" group, which consists largely of chronic brain syndromes.

Further significant basis for comparison of effectiveness is the determina-

tion of effectiveness of one drug after failure of the other. Tables 7-A, -B, and -C indicate such a comparison of effectiveness in 122 patients treated with chlorpromazine after failure of reserpine and 127 patients treated with reserpine after failure with chlorpromazine. The schizophrenic group is the only one with significant numbers, but the results in other groups are completely consistent with those in the schizophrenic group. Only 10 patients of the 127 treated with reserpine after chlorpromazine failure achieved an "A" or "B" result, while 32 of the 122 treated with chlorpromazine after reserpine failure achieved such a result. This is particularly significant among the patients who were ill for more than 2 years in the hospital.

TABLE 7-A.—EFFECT OF CHANGING FROM ONE DRUG TO THE OTHER
ALL CATEGORIES

	Reserpine after Chlorpromazine					*Chlorpromazine after Reserpine*				
Time in Hospital	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
0–2 years		1	9	7	17	3	9	15	5	32
2–5 years	1	2	13	2	18	1	9	17		27
5–10 years			19	3	22		3	11	2	16
Over 10 years		6	33	31	70		7	27	13	47

All patients treated 3 months before change-over, none achieved grade better than "C" in first treatment. Result from second treatment period tabulated.

TABLE 7-B.—SCHIZOPHRENIC

	Reserpine after Chlorpromazine					*Chlorpromazine after Reserpine*				
Time in Hospital	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
0–2 years			3	1	4	2	6	4	5	17
2–5 years	1	1	4	1	7	1	8	8		17
5–10 years			10	2	12		2	6	2	10
Over 10 years		4	24	17	45		2	16	11	29

TABLE 7-C.—MANIC-DEPRESSIVE AND INVOLUTIONAL

	Reserpine after Chlorpromazine					*Chlorpromazine after Reserpine*				
Time in Hospital	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
0–2 years				1	1	1		1		2
2–5 years		1	1		2		1	4		5
5–10 years			5	1	6		1	1		2
Over 10 years			8	7	15		4	6	1	11

TABLE 7-D.—MISCELLANEOUS

	Reserpine after Chlorpromazine					*Chlorpromazine after Reserpine*				
Time in Hospital	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
0–2 years		1	6	5	12		3	10		13
2–5 years			8	1	9			5		5
5–10 years			4		4			4		4
Over 10 years		2	1	7	10		1	5	1	7

Observation of prolonged treatment with chlorpromazine and with reserpine (Table 8), indicates that in any large group of patients continued treatment over a long period of time increases the proportion of "A" and "B" results. This "long-term" effect is more marked with chlorpromazine than with reserpine. These observations indicate that in treatment of chronic psychotic individuals, particularly in state hospital surroundings, chlorpromazine is productive of a greater proportion of patients susceptible to rehabilitation and discharge than is reserpine, but that reserpine is definitely effective.

TABLE 8.—RESULTS IN A GROUP OF PATIENTS TREATED CONTINUOUSLY WITH CHLORPROMAZINE AND A GROUP OF PATIENTS TREATED CONTINUOUSLY WITH RESERPINE, WITH GRADES OF IMPROVEMENT FOR EACH GROUP AT 3, 6, AND 9 MONTHS.

	Chlorpromazine—Schizophrenia 479					*Reserpine—Schizophrenia 43*				
Time in Hospital	*A*	*B*	*C*	*D*	*Total*	*A*	*B*	*C*	*D*	*Total*
3 MONTHS										
0–2 years	13	59	72	9	153	2	1	10	2	15
2–5 years	2	20	59	12	93		2	4		6
5–10 years	1	7	58	12	78			4	3	7
Over 10 years		1	81	73	155			9	6	15
6 MONTHS										
0–2 years	26	60	64	3	153	2	5	8		15
2–5 years	3	33	53	4	93		2	4		6
5–10 years	1	19	53	5	78		3	2	2	7
Over 10 years		12	98	45	155		1	12	2	15
9 MONTHS										
0–2 years	28	65	57	3	153	1	5	9		15
2–5 years	5	40	44	4	93	1	1	4		6
5–10 years	2	22	51	3	78		2	4	1	7
Over 10 years		21	93	41	155		1	12	2	15

USE OF MEDICATION IN ASSOCIATION WITH OTHER TREATMENT. A number of reports have already been published concerning the dangers of treatment with electro-shock in patients who are receiving chlorpromazine or reserpine. These reports in our opinion are insufficiently documented in respect to the kind of technique and the kind of electric current used in such treatment, and the use of anesthetic and protective drugs such as pentothal, atropine and succinyl choline chloride. In our own experience neither chlorpromazine nor reserpine presents any contraindication to the use of electro-shock when low intensity sine wave alternating current is administered by the true glissando technique with the use of atropine preliminary to the treatment, and without the use of any skeletal muscle relaxing agent. In the treatment of actual depressions, neither drug is dependably effective without the use of electro-shock, but the electro-shock is made more quickly and adequately effective when given in conjunction with these drugs. We are now studying results in significant numbers of patients resistant to drug and electro-shock treatment alone, who are being subjected to combination of drug and electro-shock. These results are not yet ready for report.

In the management of patients in psychotherapy, particularly in non-psychotic individuals suffering from psychoneuroses of moderate to severe degree, chlorpromazine often has the effect of mitigating panic and bringing

to light psychotic mechanisms and improving the relationship of the patient not only with the therapist but with other significant individuals in his life. Reserpine in our experience has less of this specific effect on the mechanism of communication and understanding involved in psychotherapy.

The synergism with other sedative and narcotic medication is peculiar to chlorpromazine alone. Smaller doses of barbiturate or morphine are required in patients under the influence of chlorpromazine. This property of the drug is not important in psychotic patients except with coincident malignant disease. The earlier concern with the use of chlorpromazine in patients under the influence of alcohol has not been confirmed generally. Both chlorpromazine and reserpine seem to have the effect of mitigating or preventing withdrawal symptoms on withdrawal of narcotic in addicted individuals.

Conclusions. Chlorpromazine and reserpine are both potent phrenotropic drugs. In treatment of severe psychotic illness particularly in state hospital surroundings and particularly in illness of long duration, chlorpromazine is somewhat more effective than reserpine. In milder psychotic illness and illness of short duration, such distinction in effectiveness is not clearly evident. In other aspects, particularly in toxicity and side-effects, no distinct preference for one drug or the other can be determined except in individual responses of patients to one drug or the other. In some hyper-intense or extremely resistant psychotic states, the use of the two drugs together at maximal levels is more effective than either one alone.

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SUMMARIO IN INTERLINGUA

Comparation del Effectos Clinic de Chlorpromazina e Reserpina in Patientes Psychotic

Chlorpromazina e reserpina es ambes potente drogas phrenotropic. In le tractamento de sever morbo psychotic, specialmente in le atmosphera de un hospital statal e specialmente in casos de morbo de longe duration, chlorpromazina es alique plus efficace que reserpina. In plus leve casos de morbo psychotic e in casos de morbo de plus breve durationes, nulle tal distinction del efficacia del duo drogas es clarmente evidente. In altere respectos, specialmente quanto a lor toxicitate e a lor effectos lateral, nulle distincte preferibilitate del un o del altere droga pote esser determinate, excepte super le base del responsas individual de un date patiente al un o al altere del duo drogas. In certe hyperintense o extrememente resistente statos psychotic, le uso combinate del duo drogas in doses maximal es plus efficace que le un o le altere sol.

THE RARE OCCURRENCE OF METASTATIC CARCINOMA IN THE CIRRHOTIC LIVER

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The main purpose of this report is to show that metastatic carcinoma rarely occurs in the liver with portal cirrhosis. This is in striking contrast to the fact that, of all the viscera, the liver is most frequently the site for metastatic carcinoma. The reasons for the rare occurrence of metastatic carcinoma in the liver with portal cirrhosis are obscure. In an attempt to elucidate some of these, it becomes necessary to determine the general incidence of portal cirrhosis, the general incidence of carcinoma and the coincidental occurrence of both.

Material and Method. An analysis was made of 26,895 consecutive necropsies performed at the Philadelphia General Hospital during a period of 20 years, from the beginning of 1920 to the close of 1939 and of 7,771 consecutive necropsies performed at the Jefferson Medical College Hospital from the beginning of 1920 to the end of 1949. Since both carcinoma and cirrhosis are infrequent before the age of 20 years, all necropsies on patients below this age are eliminated from consideration. Therefore, this report is based upon 24,329 necropsies from the Philadelphia General Hospital (Group 1) and 5,450 necropsies from the Jefferson Medical College Hospital (Group 2).

All cases with cirrhosis of the liver and all cases of carcinoma in various locations were recorded as to age by decades, sex and color. Included as cirrhosis of the liver were all cases of every degree with the exception of biliary cirrhosis, syphilitic cirrhosis, cardiac cirrhosis, cirrhosis associated with tuberculosis and cirrhosis associated with parasitic infestations.

INCIDENCE OF CIRRHOSIS OF THE LIVER. Cirrhosis of the liver was found in 760 cases or 3.12% of the 24,329 necropsies performed at the Philadelphia General Hospital (Group 1) and in 313 cases or 5.74% of the 5,450 necropsies performed at the Jefferson Medical College Hospital (Group 2). These figures have little value without consideration of age, sex and color. The incidence of cirrhosis differed with each of these as indicated in Table 1. In general, there was a progressive increase of cirrhosis in succeeding decades, with high peaks of incidence in Group 1 at the fifth decade in the white male, the sixth decade in both white and colored females and the seventh decade in the colored male. In Group 2, the high peaks of incidence were at the seventh decade in all except the colored male in whom this occurred at the eighth decade. The average incidence of cirrhosis was practically identical in white males and white females, namely about 4% in Group 1 and about 6% in Group 2. There was a greater incidence of cirrhosis in the colored male than in the colored female in both groups, namely, 2% and 1.3% respectively in Group 1 and 5.55% and 1.93% respectively in Group 2. This table also shows that the average incidence of cirrhosis in the colored male was about one-half that in the white male and in the colored female it was about one-third that in the white female.

THE INCIDENCE OF CARCINOMA.. Carcinoma was found in 3,826 cases or 15.72% of the 24,329 necropsies in Group 1 and 1,266 cases or 23.2% of the 5,450 necropsies in Group 2. The

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TABLE 1.—THE INCIDENCE OF CIRRHOSIS AS A NECROPSY FINDING

Age	Male White			Female White			Male Colored			Female Colored		
	Total Cases	Number with Cirrhosis	% with Cirrhosis	Total Cases	Number with Cirrhosis	% with Cirrhosis	Total Cases	Number with Cirrhosis	% with Cirrhosis	Total Cases	Number with Cirrhosis	% with Cirrhosis
Group 1 (Philadelphia General Hospital)												
20–30	358	7	1.95	392	4	1.0	685	9	1.31	925	1	0.11
30–40	733	29	3.96	554	9	1.62	900	13	1.44	891	9	1.01
40–50	1371	72	5.25	842	38	4.51	1056	28	2.65	932	18	1.93
50–60	2044	90	4.40	1139	61	5.35	961	27	2.81	807	21	2.60
60–70	2441	99	4.05	1523	76	4.99	645	10	1.55	477	5	1.05
70–80	1744	57	3.27	1267	43	3.39	307	7	2.28	256	3	1.17
80–90	515	13	2.52	375	10	2.67	65	0	0.0	44	0	0.0
90+	29	0	0.0	34	1	2.94	9	0	0.0	8	0	0.0
All cases	9235	367	3.97	6126	242	3.95	4628	94	2.03	4340	57	1.31
Group 2 (Jefferson Hospital)												
20–30	276	5	1.81	200	4	2.0	50	0	0.0	74	3	4.05
30–40	393	20	5.09	262	11	4.20	75	5	6.67	76	0	0.0
40–50	570	38	6.67	314	19	6.05	85	4	4.71	73	1	1.37
50–60	862	46	5.34	356	27	7.58	72	5	6.94	52	1	1.92
60–70	715	59	8.25	329	28	8.51	44	4	9.09	25	1	4.0
70–80	336	23	6.84	135	8	5.92	13	1	7.7	9	0	0.0
80–90	68	0	0.0	37	0	0.0	1	0	0.0	0	0	0.0
90+	2	0	0.0	2	0	0.0	2	0	0.0	1	0	0.0
All cases	3162	191	6.04	1635	97	5.93	342	19	5.55	311	6	1.93
Groups 1 & 2												
20–30	576	12	2.08	592	8	1.35	735	9	1.22	999	4	0.40
30–40	1126	49	4.35	816	20	2.45	975	18	1.85	967	9	0.93
40–50	1941	110	5.67	1156	57	4.93	1141	32	2.80	1005	19	1.89
50–60	2906	136	4.68	1495	88	5.89	1033	32	3.10	859	22	2.56
60–70	3153	158	5.01	1852	104	5.61	689	14	2.03	502	6	1.19
70–80	2081	80	3.84	1402	51	3.63	320	8	2.5	265	3	1.13
80–90	583	13	2.23	412	10	2.43	66	0	0.0	44	0	0.0
90+	31	0	0.0	36	1	2.77	11	0	0.0	10	0	0.0
All cases	12397	558	4.5	7761	339	4.37	4970	113	2.27	4651	63	1.35

incidence of carcinoma in each group varied with age, sex and color as indicated in Table 2. In Group 1, there was a progressive increase in the incidence of carcinoma to the sixth decade in colored females, the seventh decade in white males and females, and to the eighth decade in colored males. In Group 2, there was a progressive increase in the incidence of carcinoma to the seventh decade in colored females and to the eighth decade in white males, white females, and colored males. There was little difference in the average incidence of carcinoma between white males (18.8%) and white females (18.4%) in Group 1 and between white males (25.4%) and white females (22%) in Group 2. The average incidence of carcinoma in colored males in Group 1 (9.2%) was less than in colored females (12.3%), whereas in Group 2, there was little difference, namely, 16.1% and 15.1% respectively. The average incidence of carcinoma in the colored male was about one-half that of the white male in Group 1 and in the colored female, it was about two-thirds that of the white female. In Group 2, the total number of cases and total number of carcinomas in colored males and females was too small for adequate analysis.

INCIDENCE OF CIRRHOSIS OF THE LIVER AND CARCINOMA IN VARIOUS LOCATIONS. A further analysis was made to determine the incidence of cirrhosis of the liver in patients having carcinoma in various locations. Cirrhosis of the liver was found in 83 of the 3,850 cases of carcinoma (2.16%) in Group 1, and in 50 of the 1,242 cases of carcinoma (4.3%) in Group 2. The incidence of cirrhosis of the liver in patients with various carcinomas was, therefore, about 70% of that occurring in the general necropsy population. This was true in each sex of both colors in both groups. Included were 28 patients with cirrhosis and primary carcinoma of the liver or 39.4% of the total number of 71 patients with primary carcinoma of the liver in Group 1, and 16 cases or 45.7% of the total 35 cases of primary carcinoma of the liver in Group 2. Excluding these cases from consideration, there were only 55 cases (1.46%) in Group 1 and 34 cases (2.9%) in Group 2 with cirrhosis of the liver and carcinoma elsewhere in the body. Therefore, the incidence of cirrhosis of the liver in cases of primary carcinoma occurring elsewhere in the body was about one-half that occurring in the general necropsy population in both groups.

INCIDENCE OF CIRRHOSIS AND METASTATIC CARCINOMA OF THE LIVER. Only one case of metastatic carcinoma in a liver with portal cirrhosis (0.13%) was found in Group 1. This occurred in a white woman aged 60 years with primary carcinoma of the breast. There was a total of 334 cases of primary carcinomas of the breast in this group and metastases in the liver were found in 146 cases (43.7%). Carcinoma of the breast was coincident with cirrhosis of the liver in 9 cases and it was one of these which showed metastases in the liver.

There were 5 cases of metastatic carcinoma and cirrhosis of the liver (1.6%) in Group 2. One occurred in a white man aged 59 years with primary carcinoma of the sigmoid colon. This was one of 3 cases of cirrhosis of the liver coincident with primary carcinoma of the sigmoid colon and rectum, of which there was a total of 120 cases with 37 cases or 30.8% showing metastases in the liver. Another case occurred in a white man with primary carcinoma of the prostate gland. This was one of 2 cases of cirrhosis of the liver coincident with primary carcinoma of the prostate gland, of which there was a total of 66 cases, 12 or 18.1% showing

TABLE 2.—THE INCIDENCE OF CARCINOMA AS A NECROPSY FINDING

Age	*Male White*			*Female White*			*Male Colored*			*Female Colored*		
	Total Cases	*Number with Carcinoma*	*% with Carcinoma*	*Total Cases*	*Number with Carcinoma*	*% with Carcinoma*	*Total Cases*	*Number with Carcinoma*	*% with Carcinoma*	*Total Cases*	*Number with Carcinoma*	*% with Carcinoma*
Group 1 (Philadelphia General Hospital)												
20–30	358	14	3.91	392	13	3.32	685	5	0.73	925	25	2.70
30–40	733	48	6.55	554	85	15.34	900	18	2.0	891	64	7.18
40–50	1371	174	12.69	842	174	20.66	1056	75	7.10	932	158	16.95
50–60	2044	439	21.48	1139	248	21.77	961	140	14.57	807	155	19.21
60–70	2441	598	24.50	1523	340	22.32	645	118	18.30	477	85	17.82
70–80	1744	369	21.16	1267	203	16.02	307	59	19.22	256	45	17.58
80–90	515	89	17.28	375	62	16.53	65	10	15.38	44	3	6.82
90+	29	6	20.69	34	4	11.76	9	0	0.0	8	0	0.0
All cases	9235	1737	18.81	6126	1129	18.43	4628	425	9.18	4340	535	12.33
Group 2 (Jefferson Hospital)												
20–30	218	7	3.21	200	12	6.0	50	0	0.0	74	3	4.05
30–40	393	38	9.67	262	24	9.16	75	3	4.0	76	9	11.84
40–50	570	129	25.29	314	75	23.88	85	12	14.12	73	13	17.81
50–60	862	251	29.12	356	102	28.65	72	21	29.17	52	13	25.0
60–70	712	231	32.44	329	98	29.79	44	12	27.27	25	8	32.0
70–80	337	128	37.98	135	43	31.85	13	7	53.85	9	1	11.11
80–90	68	19	27.94	37	6	16.22	1	0	0.0	0	0	0.0
90+	2	1	50.0	2	0	0.0	2	0	0.0	2	0	0.0
All cases	3162	804	25.43	1635	360	22.01	342	55	16.08	311	47	15.11
Groups 1 & 2												
20–30	576	21	3.64	592	25	4.22	735	5	0.68	999	28	2.80
30–40	1126	86	7.64	816	109	13.36	975	21	2.15	967	73	7.55
40–50	1941	303	15.61	1156	249	21.54	1141	87	7.62	1005	171	17.01
50–60	2906	690	23.74	1495	350	23.41	1033	161	15.58	859	168	19.56
60–70	3153	829	26.29	1852	438	23.65	689	130	18.87	502	93	18.52
70–80	2081	497	23.88	1402	246	17.55	320	66	20.62	265	46	17.36
80–90	583	108	18.52	412	68	16.50	66	10	15.15	44	3	6.82
90+	31	7	22.58	36	4	11.11	11	0	0.0	10	0	0.0
All cases	12397	2541	20.50	7761	1489	19.18	4970	480	9.66	4651	582	12.51

metastases in the liver. The other 3 cases occurred in white men aged 42, 53 and 60 years respectively, each with primary carcinoma of the esophagus. There were 7 cases of cirrhosis of the liver coincident with a total of 83 cases of primary carcinoma of the esophagus, of which, 10 cases or 12% showed metastases in the liver. In addition to the above-mentioned 5 cases of cirrhosis and metastatic carcinoma of the liver, there were 2 cases of primary carcinoma of the gallbladder with direct extension of the neoplasm into the contiguous liver substance but metastases were not present.

A review of the histologic sections of the liver revealed tumor emboli in some of the portal venous branches in each case. Tumor cells appeared to spread into the contiguous stroma, later infiltrating the peripheries of the hepatic nodules which were gradually replaced by them. The hepatic arteries and arterioles appeared normal.

Discussion. The difference in the average incidence of cirrhosis of the liver in the two hospitals is striking, namely 3.12% in Group 1 (Philadelphia General Hospital) and 5.74% in Group 2 (Jefferson Medical College Hospital). No suggestion can be offered for this difference. The great majority of patients admitted to the Philadelphia General Hospital are indigent, chronic or aged sick, with provisions made for a small percentage of sick who are employees of the city government. About 40% of the patients admitted to the Jefferson Medical College Hospital are indigent or free ward patients, the remainder coming from all classes or income groups. This would suggest that economic status and nutrition are not very important factors affecting the incidence of cirrhosis, for poor nutrition is more frequently noted clinically at the Philadelphia General Hospital. It is generally stated in the literature that, on the average, cirrhosis of the liver is from two to three times more frequent in men than in women. My data show this to be true only in the colored patients, whereas the frequency of cirrhosis was practically the same in white males and females in each of the hospitals. However, the average incidence of cirrhosis is considerably less in the colored race than in the white race, with a ratio of 2:1 for white to colored males and about 3:1 for white to colored females.

The peak incidence of carcinoma occurred one decade later than that of cirrhosis of the liver. The average incidence of all carcinomas was approximately the same in white males and females, although the incidence for both was greater at the Jefferson Hospital. The average incidence of carcinoma in the colored male was about one-half that in the white male and in the colored female, it was about two-thirds that of the white female at the Philadelphia General Hospital. At the Jefferson Hospital, the total number of carcinomas and total cases in colored patients was too small for adequate analysis.

The average incidence of cirrhosis of the liver in patients having carcinoma in various locations exclusive of the liver was about one-half the average incidence of cirrhosis found in the general necropsy population. This was true in each sex of both colors in both hospitals. The reasons for this are obscure. A small portion of this difference may be due to the fact that the peak incidence of carcinoma occurred one decade later than that of cirrhosis of the liver.

Metastatic carcinoma of the liver occurred in 4.9% of all necropsies or 28.6% of all carcinomas in this report. Of the total of 1,865 cases of primary carcinoma arising from organs drained

by the portal venous system*, 1841 cases or 45.1% showed metastatic growths in the liver. These figures emphasize the frequent occurrence of metastatic carcinoma of the liver. There were 18 cases of metastatic carcinoma of the liver to every case of primary carcinoma of this organ. However, metastatic carcinoma rarely occurred in the cirrhotic liver, with only one case in 24,329 necropsies in Group 1 and 5 cases in 5,450 necropsies in Group 2, or 0.12% of all carcinomas.

A review of the literature disclosed 19 cases of metastatic carcinoma in cirrhotic livers. The first reported observation was in 1888 by Hanot and Gilbert[3], the case being restudied and reported by Poulain[7] as occurring in a 68-year-old woman with primary carcinoma of the stomach. Achard and Laubry[1] described a 65-year-old man with primary carcinoma of the ascending colon. Colwell[2] reported 2 cases occurring in 2,634 necropsies, one in a 69-year-old man with a primary tumor of the orbit and the other in a 58-year-old woman with carcinoma of the breast. Rabl[8], in a series of carcinomas of the stomach found 3 cases with coincident cirrhosis of the liver. Lisa, Solomon and Gordon[5] published 6 cases occurring as follows: a primary carcinoma of the papilla of Vater, 2 cases of carcinoma of the stomach, 2 cases of carcinoma of the pancreas and 1 case of carcinoma of the esophagus. These 6 cases of secondary carcinoma and cirrhosis of the liver occurred in 6,036 necropsies. In 6,356 necropsies performed at the Mayo Clinic, Torres[10] found 2 cases of metastatic carcinoma in cirrhotic livers, the first in a primary carcinoma of the tongue and the second in a primary carcinoma of the breast. Speert[9] in reporting on 12 cases of primary carcinoma of the uterine fundus found four of these associated with cirrhosis of the liver. One of the latter occurred in a white woman aged 53 years, the liver also containing metastatic necrotic tumor nodules. Finally, Wallach, Hyman and Angrist[11] reported that in a series of 10,156 necropsies, they found 441 cases of cirrhosis, 67 of which had concomitant cancer and in three of the latter, metastatic cancer was also found in the liver. The first case occurred in a 68-year-old white man with primary carcinoma of the stomach, the second case in a 72-year-old white man with primary carcinoma of the esophagus and the third case in a 61-year-old white female with primary carcinoma of the cecum.

The reasons for the rare occurrence of metastatic carcinoma in the cirrhotic liver are obscure and conjectural. A number of probable factors may be operative either singly or in combination. One factor may be the infrequent occurrence of hepatic cirrhosis in carcinoma of other organs, as pointed out by Lisa, Solomon and Gordon[5]. In the present study, it was found that the incidence of hepatic cirrhosis in cases of primary carcinoma elsewhere in the body was about one-half that occurring in the general necropsy population. Wallach, Hyman and Angrist[11] suggest that when both diseases are present, the duration of life may be too short for metastasis to occur. They also propose that the cirrhotic liver is an unfavorable site for growth of metastatic tumor cells by virtue of altered blood and lymphatic circulation and biliary flow, and because of other metabolic and enzymatic changes which are not as yet well understood. Alterations in vascular relationships and the fibrosis within the liver appear to me to be more important and tan-

*The portal venous system drains the lower end of the esophagus, the gastrointestinal tract with the exception of the anus, the gallbladder, bile ducts, pancreas and spleen.

gible as causal factors. The dissemination of secondary growths in the liver, unlike the spread of carcinoma elsewhere, is mainly embolic by way of the intrahepatic blood vessels and most commonly through the portal venous bed. Tumor cells extend chiefly along the sinusoidal and extrasinusoidal tissue spaces between the columns of liver cells then extending into the surrounding parenchyma in all directions. However, in cirrhosis, most of the sinusoids are obliterated, the central and hepatic veins usually being displaced to the periphery of the regenerating nodules of hepatic cells. Though some of the sinusoids remain open, portal blood may be diverted through the central and hepatic veins into the inferior vena cava without first coming into close relationship with the hepatic cells. In other words, an internal porto-caval shunt is formed (Kelty, Baggenstoss and Butt)[4]. According to McIndoe[6], in advanced cirrhosis, the total vascularity of the liver is much diminished with many of the portal trunks attenuated and stenosed and the smallest vessels distorted beyond belief. It is conceivable that these changes furnish a mechanical impediment to the usual type of embolization and spread of cancer in the liver. Another factor may be the fibrosis *per se*. During the process of development of portal cirrhosis, there is collapse, displacement and condensation of the reticulum of the parenchyma. Each recurrent episode of hepatic injury leads to subsequent nodular repair, followed by collapse and condensation of more and more reticulum which is then represented by thick connective-tissue bands between the remaining nodules of parenchyma and surrounding the portal radicles. These thick fibrous trabeculae probably serve further to impede or prevent the growth and spread of neoplastic cells.

Summary and Conclusions. The incidence of cirrhosis of the liver varied in the two hospitals reported upon, namely 3.12 and 5.74% of all necropsies performed on patients more than 20 years of age. The incidence varied with age, sex and color. The frequency of cirrhosis was practically identical in white men and women, but was greater in the colored man than in the colored woman. The average incidence of cirrhosis was considerably greater in the white race than in the colored race, with a ratio of 2:1 for white to colored men and about 3:1 for white to colored women.

The incidence of carcinoma in patients 20 years of age or more was 15.12% at one hospital and 23.2% of all necropsies at the other hospital. The incidence of carcinoma also varied with age, sex and color. There was little difference in the average incidence of carcinoma in white men and women at either hospital and the same was found in colored males and females. However, the average incidence of carcinoma in the colored male was about one-half that of the white male, and in the colored female it was about two-thirds that of the white female at one hospital where the total number of cases was sufficient for adequate analysis. The peak incidence of carcinoma occurred one decade later than that of cirrhosis.

The average incidence of cirrhosis of the liver in patients having carcinoma in various locations exclusive of the liver was about one-half that occurring in the general necropsy population.

Metastatic carcinoma of the liver was frequent (28.6% of all carcinomas). However, metastatic carcinoma in the liver with portal cirrhosis was rare (0.12% of all carcinomas). Nineteen such cases were found in the literature, to which this report added 6 new cases. A number of causes or factors for this rare occurrence were proposed, namely,

the infrequent occurrence of hepatic cirrhosis in carcinoma elsewhere in the body, the shortened life span in the presence of the simultaneous occurrence of both diseases, altered metabolic and enzymatic changes in the liver, alterations in vascular relationships with attenuation and stenosis of the portal venous branches, producing a mechanical impediment to the usual type of embolization and spread of cancer in the liver, and the formation of thick fibrous trabeculae further serving to impede or prevent the growth and spread of neoplastic cells.

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(Interlingua on page 181)

SUMMARIO IN INTERLINGUA

(See page 121 for original article)

Le Concentration Osmotic de Urina in le Stato Hydropenic Como Mesura del Function Reno-Tubular
Un Test pro le Detection Precoce de Disturbationes Renal
Reporto Preliminari

1. Le maximal concentration urinari in stato hydropenic esseva examinate in 32 individuos normal, 27 patientes con hypertension essential, 13 patientes con diabete mellite, e 7 patientes con compensate morbo cardiac rheumatic.

2. Le absentia de un correlation del gravitate specific del urina con su concentration osmotic es attribuibile al facto que solutos, proteina, sucro, temperatura, pH, etc. ha differente effectos super le gravitate specific e super le pression osmotic.

3. Patientes capace a elaborar concentrationes urinari de 800 mOsm/l o plus esseva considerate como possedente un adequate function renal. Patientes con inter 600 e 800 mOsm/l esseva considerate como possedente un bon function renal. Inter 400 e 600 mOsm/l, le function renal esseva considerate como non mal, e 400 mOsm/l o minus esseva considerate como indication de sever morbo renal.

4. Le test usate pote servir como un graduate methodo quantitative pro evalutar le function tubular e pro sequer le curso de morbo renal, specialmente in patientes con minimal disturbationes tubular.

5. Esseva constatate per medio del methodo un reducite function concentratori in patientes con hypertension essential e diabete mellite ante le alteration de altere communmente usate essayos del function urinari e ante le constatation clinic de signos suspecte de morbo renal.

THE EFFECTS OF NARCOTIC ANALGETICS AND NARCOTIC ANTAGONISTS ON RESPIRATION

By F. F. Foldes, M.D.

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and

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It was shown by Swerdlow, Foldes and Siker[8] that in unanesthetized subjects the narcotic antagonist levallorphan (*l*-3-hydroxy-N-allylmorphinan) tartrate, now known as Lorfan tartrate, offers considerable protection against respiratory depression caused by alphaprodine (1,3-dimethyl-4-phenyl-4-propionoxypiperidine) hydrochloride, also known under the trade name Nisentil hydrochloride. Subsequently, Foldes *et al.*[6] demonstrated that levallorphan used in combination with alphaprodine for supplementation of N_2O-O_2-Pentothal (thiopental) sodium anesthesia prevented to a marked degree the respiratory depressing effects of even large doses of this narcotic analgetic. Similarly, Ergin *et al.*[3] and Foldes *et al.*[5] used levallorphan successfully to prevent respiratory depression induced by Demerol (meperidine) hydrochloride and Rol-7113* respectively, in patients who received these narcotic analgetics for supplementation of N_2O-O_2-thiopental anesthesia. Furthermore, Backner, Foldes and Gordon[1] found that a premixed solution of alphaprodine and levallorphan is an effective and safe analgetic in obstetrics which, in contrast to other forms of analgesia, does not produce respiratory or circulatory depression of either mother or child. Finally, Foldes[4] used levallorphan to re-establish spontaneous respiration in patients who had been rendered apneic with narcotic analgetics when mechanical control of respiration by means of ventilators was employed in abdominal and thoracic surgery.

In view of the wide applicability of levallorphan in anesthetized patients, it seemed desirable to extend further the original controlled studies of the effects of alphaprodine and levallorphan on respiration[8] to include lightly anesthetized patients. The investigations thus inaugurated included two narcotic analgetics, namely, meperidine (1-methyl-4-phenyl-4-carbethoxypiperidine) and alphaprodine, and two narcotic antagonists, namely, levallorphan and nalorphine. The latter, which chemically is N-allylnormorphine, is also known as Nalline or Lethidrone.

Material and Method. The present study comprises a total of 110 subjects (62 males and 48 females), whose ages ranged from 17 to 73 years (average 44 years) and who underwent surgery under subarachnoid or epidural block, not extending above the 10th dorsal dermatome. All patients were premedicated with 50 to 200 mg. of pentobarbital (Nembutal) sodium, given orally 60 to 90 minutes preoperatively and with a combination of 50 to 100 mg. of meperidine and 0.3 to 0.4 mg. of scopolamine or 0.4 to 0.6 mg. atropine, injected intramuscularly 45 to 60 minutes prior to administration of regional anesthesia.

*Rol-7113 is 1-methyl-3-allyl-4-phenyl-4-propionoxypiperidine hydrochloride.

On arrival in the operating room the patient's mouth and pharynx were sprayed with a 1% tetracaine (Pontocaine) hydrochloride solution and an intravenous infusion of 5% dextrose in water or saline was instituted. After the regional block was established, the patients received intravenously a sleeping dose of thiopental sodium. These, as well as all subsequent injections, were administered through the rubber sleeve of the infusion tubing. Following the insertion of an oropharyngeal airway, a 4 liter to 1 liter nitrous oxide-oxygen mixture was administered by face mask. The breathing bag of the anesthesia machine was allowed to fill up with this mixture 3 to 4 times in succession. When the level of general anesthesia became stabilized, the administration of nitrous oxide-oxygen was continued in a 500 ml. to 500 ml. ratio.

When the respirations had become fairly regular, control values of minute volume were determined by means of a Bennett ventilation meter inserted on the inspiratory side of the circle absorption system. Control values of respiratory rates, pulse rates and blood pressure readings were also obtained.

The patients were divided into four groups of 40, 30, 20 and 20 patients respectively. In these groups, the effects of the following drugs on respiratory function were studied: meperidine and levallorphan; alphaprodine and levallorphan; meperidine and nalorphine; and alphaprodine and nalorphine.

The doses of these drugs used in all experiments were: 2 mg./kg. of meperidine, 0.66 mg./kg. of alphaprodine, 0.03 mg./kg. of levallorphan and 0.15 mg./kg. of nalorphine. The four main groups were further divided into a total of 11 subgroups of equal size. Thus, 10 patients each received the medications listed below in the sequences indicated.

MEPERIDINE-LEVALLORPHAN.

1) At zero time, meperidine followed at 31 minutes by levallorphan.
2) At zero time, meperidine followed at 4 minutes by levallorphan.
3) At minus 5 minutes, levallorphan followd at zero time by meperidine.
4) At zero time, meperidine plus levallorphan, premixed.

ALPHAPRODINE-LEVALLORPHAN.

5) At zero time, alphaprodine followed at 31 minutes by levallorphan.
6) At zero time, alphaprodine followed at 4 minutes by levallorphan.
7) At minus 5 minutes, levallorphan followed at zero time by alphaprodine.

MEPERIDINE-NALORPHINE.

8) At zero time, meperidine followed at 4 minutes by nalorphine.
9) At minus 5 minutes, nalorphine followed at zero time by meperidine.

ALPHAPRODINE-NALORPHINE.

10) At zero time, alphaprodine followed at 4 minutes by nalorphine.
11) At minus 5 minutes, nalorphine followed at zero time by alphaprodine.

Meperidine and Alphaprodine were administered in 30 seconds and levallorphan and nalorphine were injected as rapidly as feasible.

The respiratory control measurements were taken just before zero time except for Subgroups 3, 7, 9 and 11, in which they were taken just before "minus 5 minutes." Further respiratory readings were recorded at 3, 7, 10, 15, 20 and 30 minutes. Moreover, in Subgroups 1 and 5 these measurements were taken also at 34 minutes, that is, 3 minutes after the administration of levallorphan, and in Subgroups 3, 7, 9 and 11, at "minus one minute," that is, 4 minutes after injection of the narcotic antagonists. From the minute volumes and respiratory rates obtained, tidal volumes and alveolar ventilation rates were calculated. In these calculations the total dead space (physiological dead space plus the dead space of the mask) was assumed to be 200 ml. All findings were expressed in per cent of control values. Pulse rates and blood pressure readings were taken at approximately the same times when respiratory measurements were carried out. Observations on the state of consciousness of the patients were also made. At the end of the experiments the subjects were allowed to breathe 100% oxygen for 60 to 90 seconds, whereupon the face mask was removed.

Respiratory tracings were recorded of eight subjects who received medication in accordance with the sequences and timing of Subgroups 2, 3, 6, 7, 8, 9, 10 and 11.

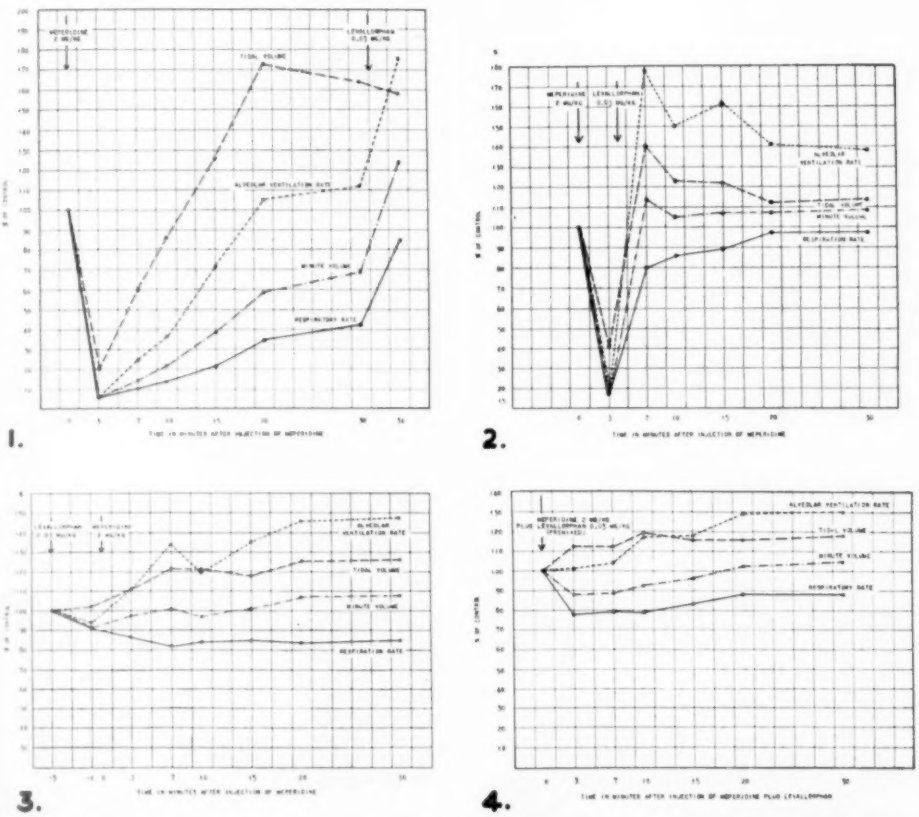
Results. Figures 1 to 11 show the average findings of respiratory rate, minute volume, tidal volume and alveolar ventilation rate in the 11 Subgroups of patients studied.

EFFECTS OF MEPERIDINE ALONE AND ALPHAPRODINE ALONE ON RESPIRATION.

Subgroup 1. Meperidine produced apnea in 8 of the 10 patients within an average of 75 seconds. Spontaneous respiration returned within an average

of 11.5 minutes. As is seen from Fig. 1, the averages of respiratory rate and minute volume were still significantly reduced at 30 minutes. Tidal volume and alveolar ventilation rate were adversely affected for only shorter periods of time.

tion returned before the administration of levallorphan in 6 patients within an average of 20.5 minutes. In the remaining 4 subjects, spontaneous respiration was resumed only after injection of the narcotic antagonist. As is seen from Fig. 5, the averages of respiratory rate,

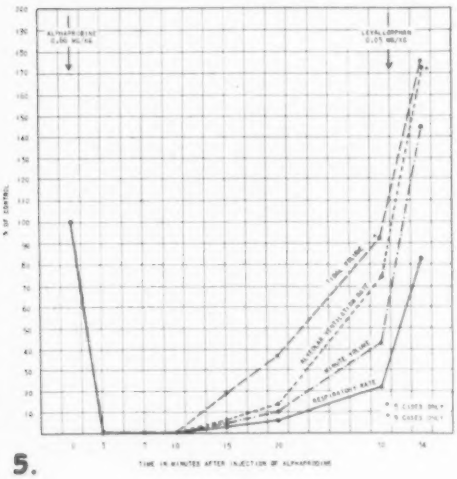


Average values of respiratory measurements for 40 patients, of whom 10 subjects each were given at the times indicated: Meperidine (Demerol) followed by levallorphan (Lorfan), Fig. 1; meperidine followed by levallorphan, Fig. 2; levallorphan followed by meperidine, Fig. 3; and meperidine plus levallorphan premixed, Fig. 4.

Subgroups 2 and 8. It is evident from Figs. 2 and 8 that, also in these Subgroups, meperidine depressed respiration very markedly.

Subgroup 5. Alphaprodine produced apnea in all 10 patients within an average of 72 seconds. Spontaneous respiration returned before the administration of levallorphan in 6 patients within an average of 20.5 minutes. In the remaining 4 subjects, spontaneous respiration was resumed only after injection of the narcotic antagonist. As is seen from Fig. 5, the averages of respiratory rate, minute volume and alveolar ventilation rate, but not of tidal volume were still significantly reduced at 30 minutes.

Subgroups 6 and 10. It is evident from Figs. 6 and 10 that, also in these Subgroups, alphaprodine depressed respiration very markedly.



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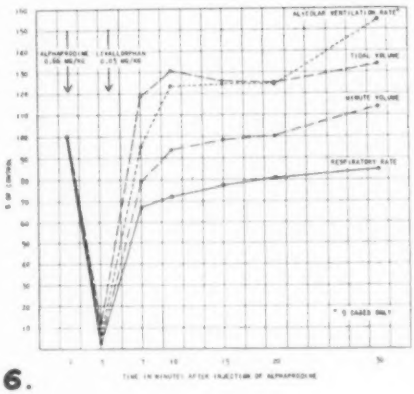

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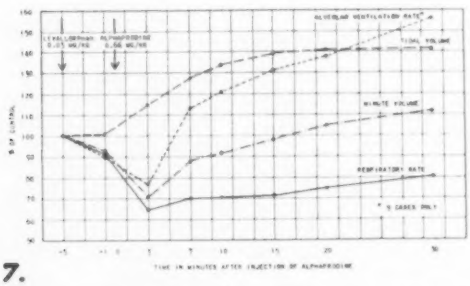
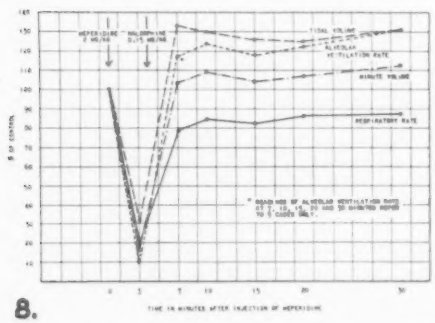


7.

Average values of respiratory measurements for 30 patients, of whom 10 subjects each were given at the times indicated: Alphaprodine (Nisentil) followed by levallorphan (Lorfan), Fig. 5; alphaprodine followed by levallorphan, Fig. 6; and levallorphan followed by alphaprodine, Fig. 7.



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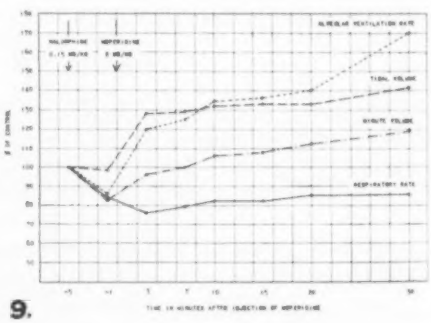


9.

Average values of respiratory measurements for 20 patients, of whom 10 subjects each were given at the times indicated: Meperidine (Demerol) followed by nalorphine (Nalline), Fig. 8 and nalorphine followed by meperidine, Fig. 9.

EFFECTS OF LEVALLORPHAN ALONE AND NALORPHINE ALONE ON RESPIRATION. *Subgroups 3 and 7.* As is seen from Figs. 3 and 7, levallorphan produced a slight depression of the averages of respiratory rate, minute volume, and alveolar ventilation rate, but not of tidal volume, 4 minutes after injection.

Subgroups 9 and 11. It is evident from Figs. 9 and 11 that the effects of nalorphine on respiration were quite similar to those of levallorphan.

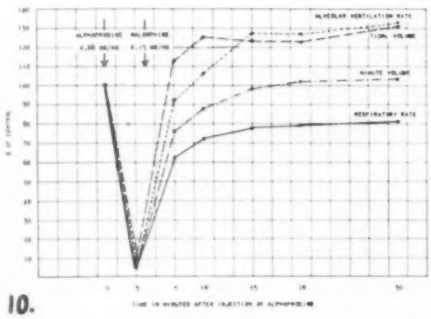
EFFECTS OF LEVALLORPHAN AND NALORPHINE ON MEPERIDINE AND ALPHAPRODINE-INDUCED RESPIRATORY DEPRESSION. *Subgroups 2 and 6.* As is seen from Figs. 2 and 6, meperidine- and alphaprodine-induced respiratory depression were dramatically antagonized by the injection of levallorphan.

LEVALLORPHAN FOLLOWING MEPERIDINE. Three minutes after administration of levallorphan and at all subsequent readings, the averages of minute volume, tidal volume, and alveolar ventilation rate were above 100% of control. The averages of respiratory rate recorded after administration of levallorphan ranged from 80 to 97% of control.

LEVALLORPHAN FOLLOWING ALPHAPRODINE. The averages of respiratory rate, recorded after levallorphan administration, ranged from 68% to 85%. At the first two readings after injection of levallorphan, the averages of minute volume were 80% and 94% of control, and at 11 and 16 minutes after antagonist administration they were practically 100% of control. At 26 minutes after levallorphan, the average minute volume was above control value. On all occasions when readings were taken after levallorphan administration, the averages of tidal volume and alveolar ventilation rate were above control values, with the exception of the alveolar ventilation rate 3 minutes after levallorphan.

Subgroups 1 and 5. It is evident from Figs. 1 and 5 that, also in these Subgroups, levallorphan counteracted meperidine- and alphaprodine-induced respiratory depression promptly.

Subgroups 8 and 10. As is seen from Figs. 8 and 10, meperidine- and alphaprodine-induced respiratory depression were as dramatically antagonized by the injection of nalorphine as they were by the injection of levallorphan. The curves are quite similar to those obtained in the experiments in which levallorphan was given 4 minutes after the narcotic analgetics (Figs. 2 and 6).



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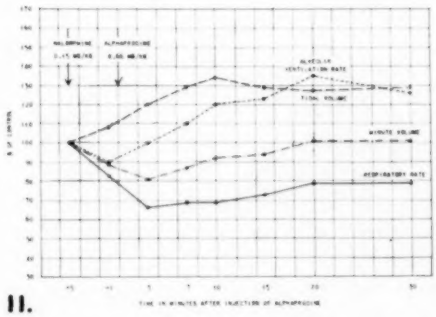


11.

Average values of respiratory measurements for 20 patients, of whom 10 subjects each were given at the times indicated: Alphaprodine (Nisentil) followed by nalorphine (Nalline), Fig. 10; and nalorphine followed by alphaprodine, Fig. 11.

EFFECTS OF LEVALLORPHAN AND NALORPHINE IN PREVENTING MEPERIDINE- AND ALPHAPRODINE-INDUCED RESPIRATORY DEPRESSION. *Subgroups 3 and 7.* As is seen from Figs. 3 and 7, levallorphan prevented both meperidine- and alphaprodine-induced respiratory depression to a very considerable degree.

LEVALLORPHAN PRECEDING MEPERIDINE. The averages of respiratory rate recorded after the administration of meperidine ranged from 82 to 87% of control; the averages of minute volume from 97 to 108% of control; the averages of tidal volume from 111 to 126% of control; and the averages of alveolar ventilation rate from 112 to 149% of control.

LEVALLORPHAN PRECEDING ALPHAPRODINE. The averages of respiratory rate, recorded after the administration of alphaprodine, ranged from 65% to 80% of control; the averages of minute volume from 71% to 113% of control; the averages of tidal volume from 115% to 142% of control; and the averages of alveolar ventilation rate from 77% to 158% of control.

Subgroups 9 and 11. As is seen from Figs. 9 and 11, also nalorphine prevented both meperidine- and alphaprodine-induced respiratory depression to a very considerable degree. The curves are quite similar to those obtained in the experiments in which levallorphan preceded these narcotic analgetics (Figs. 3 and 7).

EFFECTS OF MEPERIDINE AND LEVALLORPHAN (PREMIXED) ON RESPIRATION.* *Subgroup 4.* It is evident from Fig. 4 that the premixed solution of meperidine and levallorphan did not produce marked depression of respiratory function. Thus, the averages of respiratory rate ranged from 78 to 88% of control; the averages of minute volume from 88 to 104% of control; the averages of tidal volume from 112 to 119% of control; and the averages of alveolar ventilation rate from 101 to 130% of control.

EFFECTS OF DRUGS ON RESPIRATORY TRACINGS. Figures 12 to 15 are representative respiratory tracings of subjects who received: meperidine followed by levallorphan (Subgroup 2); levallorphan followed by alphaprodine (Subgroup 7); meperidine followed by nalorphine (Subgroup 8); and nalorphine followed by alphaprodine (Subgroup 11).

As can be seen from these graphs, both levallorphan and nalorphine antagonized or prevented meperidine- and alphaprodine-induced respiratory depression, depending on the sequence of drug administration.

EFFECTS OF DRUGS ON PULSE RATE AND BLOOD PRESSURE. Significant changes of pulse rates and blood pressure readings did not occur.

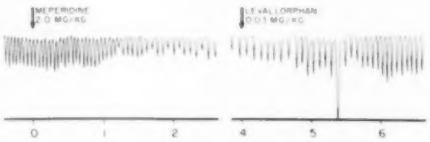
EFFECTS OF DRUGS ON PATIENT REACTIVITY. The majority of patients who had received alphaprodine and levallorphan or nalorphine were capable of answering questions five minutes after termination of nitrous oxide-oxygen administration, regardless of the sequence in which the narcotic analgetic and narcotic antagonist were given. However, the reactivity of patients who had received meperidine and levallorphan or nalorphine was far less satisfactory.

Discussion. It was previously shown[5] that in unanesthetized subjects, 1 mg./kg. of alphaprodine given intravenously caused marked respiratory depression, without, however, producing apnea. In contrast, it was demon-

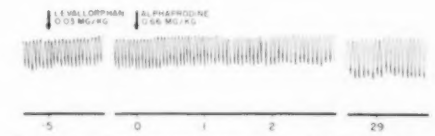
*Our original plan called also for the investigation of the effects of alphaprodine-levallorphan, meperidine-nalorphine and alphaprodine-nalorphine mixtures in 10 patients each. Since the results in a few cases simulated those obtained with the combined administration of meperidine and levallorphan, these three phases of the program were not completed.

strated in the present study that, in lightly anesthetized patients, an even smaller dose of alphaprodine (0.66 mg./kg.), injected by the same route, caused apnea in all 10 patients of Subgroup 5 and in 9 of the 10 patients of Subgroup 6. This proves that a sleeping dose of thiopental, or the administration of nitrous oxide-oxygen, or both, increases considerably the sensitivity of patients to the respiratory depressing effect of alphaprodine. Furthermore, it was previously shown[8] that, in unanesthetized subjects, the intravenous administration of 0.04 mg./kg. of levallorphan, given after 1 mg./kg. of alphaprodine (1:25 ratio), resulted in a return of the respiratory measurements to nearly control values. In the present study it was demonstrated that, in lightly anesthetized patients, 0.03 mg./kg. of levallorphan injected intravenously after the administration of 0.66 mg./kg. of alphaprodine (1:22 ratio), counteracted narcotic-induced respiratory depression which was more profound than that which occurred in the unanesthetized subjects. This attests to the ability of levallorphan to restore respiratory function even in subjects whose sensitivity to alphaprodine is increased.

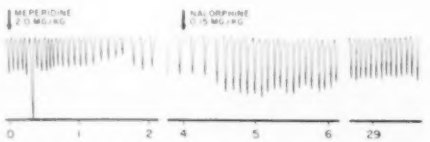
Another proof of the effectiveness of levallorphan is the fact that it counteracted respiratory depression just as dramatically in patients who had been apneic for a prolonged period and who had been deliberately hypoventilated to allow an increase of alveolar CO_2 tension (Subgroups 1 and 5), as it did in subjects in whom CO_2 accumulation had not occurred (Subgroups 2 and 6).



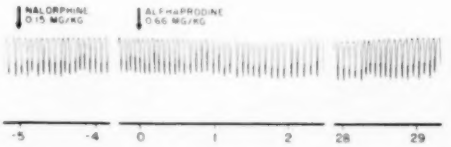
12. TIME IN MINUTES AFTER INJECTION OF MEPERIDINE



13. TIME IN MINUTES AFTER INJECTION OF ALPHAPRODINE



14. TIME IN MINUTES AFTER INJECTION OF MEPERIDINE



15. TIME IN MINUTES AFTER INJECTION OF ALPHAPRODINE

Respiratory tracings of patients who were given at the times indicated: Meperidine (Demerol) followed by levallorphan (Lorfan), Fig. 12; levallorphan followed by alphaprodine (Nisentil), Fig. 13; meperidine followed by nalorphine (Nalline), Fig. 14; and nalorphine followed by alphaprodine, Fig. 15.

Eckenhoff *et al.*[2], in their studies of the effect of levallorphan on *l*-Dromoran-induced respiratory depression in unanesthetized subjects, utilized stimulus-response type measurements and concluded that mixtures of these two agents are not capable of preventing respiratory depression normally produced by *l*-Dromoran. In contrast, Thomas and Tenney[9], who employed similar methods in normal persons, found that the antagonistic effect of levallorphan is most apparent when the respiratory mechanism is subjected

to an increased drive by CO_2. Landmesser *et al.*[7], who also employed stimulus-response type measurements, but used anesthetized patients, found that levallorphan is effective in antagonizing the depression of respiration produced by *l*-Dromoran or morphine. Although in our studies determinations of alveolar CO_2 tension or of plasma CO_2 tension were not carried out, it is quite obvious from the immediate and marked increase of respiratory function under circumstances which undoubtedly lead to increased alveolar CO_2 tension, that in lightly anesthetized patients levallorphan overcomes narcotic-induced depression if the respiratory system is under the drive of CO_2 accumulation (see above). However, the question of the effectiveness of narcotic antagonists in anesthetized patients with increased alveolar CO_2 tension is only of academic interest since in these situations minute volume and alveolar ventilation are controlled by the anesthetist. Provided that the alveolar ventilation rate is kept at normal, or above normal levels and the accumulation of CO_2 in the anesthetic equipment is prevented by CO_2 absorbers or by the use of non-rebreathing systems, increased CO_2 tensions are not likely to be encountered. Moreover, since the possible untoward effects of CO_2 accumulation and of a decrease of plasma pH have become generally recognized, it is more likely that patients are hyper- rather than hypoventilated during anesthesia. Consequently, a decrease of alveolar CO_2 tension and an increase of plasma pH are more apt to occur than the reverse.

The mechanism of action of narcotic antagonists cannot be explained fully because of inadequate knowledge of cellular pharmacology. However, competition of narcotic analgetics and antagonists for cell sites (receptors) may serve as a working hypothesis. According to this theory, the affinity of narcotic analgetics is greater for receptors of the sensory cortex than for receptors of the respiratory center and the reverse is true of narcotic antagonists.

Thus, after a moderate dose of a narcotic analgetic, many receptors of the sensory cortex, but only a few of the respiratory receptors, are occupied; and there is analgesia with little or no respiratory depression.

After a large dose of a narcotic analgetic, both types of receptors are occupied, and analgesia is accompanied by respiratory depression.

Administration of a narcotic antagonist after a large dose of a narcotic analgetic results in displacement of analgetic from most respiratory and some sensory receptors. There is alleviation of respiratory depression accompanied by moderate decrease of analgesia.

Summary. From the data presented the following facts are evident regarding patients who are lightly anesthetized with thiopental and nitrous oxide-oxygen:

Either 2 mg./kg. of Demerol (meperidine) or 0.66 mg./kg. of Nisentil (alphaprodine), that is, approximately equi-analgetic doses, markedly decrease respiratory function. This depressing effect is more profound and prolonged after the administration of alphaprodine than of meperidine. Respiratory rate is consistently affected to a greater degree than tidal volume, minute volume and alveolar ventilation rate.

Either 0.03 mg./kg. of Lorfan (levallorphan) or 0.15 mg./kg. of Nalline (nalorphine), given without narcotic, produces a slight depression of respiratory rate, minute volume and alveolar ventilation rate, 4 minutes after injection.

The aforementioned doses of levallorphan or nalorphine, given 4 minutes

after 2 mg./kg. of meperidine or 0.66 mg./kg. of alphaprodine, promptly counteract the respiratory depression caused by these narcotic analgetics. The effect on respiratory rate is less pronounced than that on the other parameters studied. Meperidine-induced depression might be somewhat more markedly antagonized than alphaprodine-induced depression.

Similarly, levallorphan or nalorphine, given 5 minutes prior to meperidine or alphaprodine, prevents respiratory depression to a considerable degree. Again, this protective effect of the narcotic antagonists may be somewhat more pronounced against meperidine than against alphaprodine depression.

Finally, levallorphan administered conjointly with meperidine in the doses studied, prevents the marked respiratory depression produced by the latter drug when given alone.

ACKNOWLEDGMENT: The Nisentil hydrochloride and Lorfan tartrate used in this study were supplied through the courtesy of Dr. Leo A. Pirk of Hoffmann-La Roche, Inc., of Nutley, New Jersey.

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(Interlingua on page 185)

CARBONIC ANHYDRASE ACTIVITY IN BLOOD OF PATIENTS WITH CHRONIC RESPIRATORY DISEASE*

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The enzyme carbonic anhydrase which is present in red blood cells and many other tissues is related to exchange of carbon dioxide (Roughton[8]). In the pulmonary capillaries the enzyme accelerates the dehydration of carbonic acid in the red blood cell ($H_2CO_3 \rightleftarrows H_2O + CO_2$). This reaction makes more CO_2 available for expiration. The present study was undertaken to determine whether patients with chronic respiratory obstruction (and elevated serum CO_2) have a compensatory increase in red blood cell carbonic anhydrase.

Methods and Material. The method used for blood analysis of carbonic anhydrase was based on Maren's modification[6] of Philpot and Philpot's method[7]. The following changes were introduced. The end point was determined visually rather than photoelectrically. The pressure of flow of CO_2 into the reaction vessel was measured by a mercury manometer and adjusted to 40 mm. of Hg. Five to 10 mm. of Hg variations in pressure gave insignificant changes in reaction time with this method. The water bath was kept at 0.2 to 0.3° C. by addition of ice and stirring with an air bubbler. An increase of 0.2° C. caused reaction times to decrease appreciably. A 1:100 dilution of oxalated whole blood in distilled water was made and 0.6 ml. of this was used in the reaction vessel (an 18 × 150 mm. test tube). The reaction vessel was equilibrated for 2 minutes with CO_2 and was changed with each determination. All solutions were placed in ice water during the procedure and the samples were immersed in ice water for 3 minutes before equilibration. The stock Na_2CO_3 was made up fresh each day from a supersaturated solution. An enzyme unit was defined as that amount of blood which would decrease the control reaction time by one-half.

With blood as a source of carbonic anhydrase the pH of the reaction was plotted against time and the shape of the curve was similar to the curves obtained by Wilbur and Anderson[10] for purified carbonic anhydrase in veronal buffer. In addition, purified blood carbonic anhydrase (method B, Keilin and Mann[4]) gave a similar curve in the system used. All determinations were done in duplicate and the average value used. The duplicate determinations did not differ more than one second which was about 3% error. Ten specimens repeated at varying intervals averaged 2.1% error (the greatest was 6.6%). Diluted specimens were stable up to at least 3 months if refrigerated. Refrigerated whole blood was stable for at least 24 hours.

Control patients were chosen at random from two hospitals. Patients with anemia were not used. Patients with respiratory disease of varying types (see Table 2) were chosen from the same source and classified prior to running of the determinations. The sex was predominantly male. The severity of the respiratory disease varied from recent asthmatic attacks to severe chronic emphysema. Three patients with dyspnea from congestive heart disease were also studied.

Results. Patients with chronic respiratory disease did not have elevated red blood cell carbonic anhydrase levels (see Fig. 1 and Table 1). The 39 control patients had levels of carbonic anhydrase ranging between 262 and 360 units per ml. of whole blood. The mean was 330.0 and the standard deviation of the mean was 24.0. Seventeen patients with respiratory disease ranged from 269 to 394 with a mean of 334.3 (standard deviation 29.5) (see Table 1). The standard error of the difference is 8.09 and, therefore, the difference is not significant. There appeared to be a slight

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increase in carbonic anhydrase levels in the older-aged patients, when the age was plotted against carbonic anhydrase per ml. of red blood cell. The r value was +.559 ($p<.001$). The CO_2-combining power of the serum in 11 patients with respiratory disease was relationship between the degree of illness and the value found. Three of the respiratory group were patients with chronic dyspnea secondary to cardiac decompensation. Their values (374, 338, 322 units/ml. of blood) were not unusual.

TABLE 1.—SUMMARY OF CARBONIC ANHYDRASE VALUES IN THE TWO GROUPS

Patients	*No.*	*Mean Carbonic Anhydrase (units/ml. blood)*	*S.D. of Mean*	*Range*	*"t" Value*
Control Group	39	330.0	24.0	262–360	.013
Respiratory Disease	17	334.3	29.5	269–364	

TABLE 2.—SUMMARY OF CLINICAL FINDINGS IN THE RESPIRATORY OBSTRUCTION GROUP

Patient	*Sex*	*Age*	*Hematocrit*	*CO_2 mEq./L.*	*Ca/ml. Whole Blood*	*Ca/ml. rbc*	*Diagnosis*
1	M	27	49		341	695	Intermittent severe asthma
2	M	34	40		322	805	Chr. rheumatic heart disease
3	M	38	59	31	367	628	Chr. asthma
4	M	50	40	42	325	814	Cor pulmonale, moribund
5	M	58	50	29	282	564	Chr. emphysema
6	M	58	45		342	760	Asthma and hypertensive failure
7	M	60	45		317	705	Tracheal obstruction
8	M	60	45	23	342	759	Chr. emphysema and cardiac failure
9	M	60	45		333	739	Chronic pul. fibrosis
10	M	60	52		374	711	Cardiac failure 18 months
11	M	61	53	29	336	635	Chr. emphysema
12	M	68	55	37	394	717	Severe pul. emphysema
13	M	73	42	28	358	852	Chr. asthma, pleural effusion
14	F	75	28	38	269	942	Miliary tbc.
15	M	78	34		296	871	Chr. emphysema and bronchitis
16	M	78	45		338	751	Cardiac dyspnea
17	F	79	43	29	348	811	Chr. pulmonary fibrosis

compared with units of carbonic anhydrase per ml. of whole blood and ml. of red blood cell (see Table 2). No trend was evident. Fourteen of the respiratory patients had dyspnea on the basis of asthma, pulmonary fibrosis or emphysema. There was no apparent

In Figs. 2 and 3 the values obtained for whole blood and for red blood cell content are plotted against the hematocrits. The activity per ml. of red blood cells decreases roughly proportional to the hematocrit ($r = -.64$, $p<.001$). There was slight increase in whole

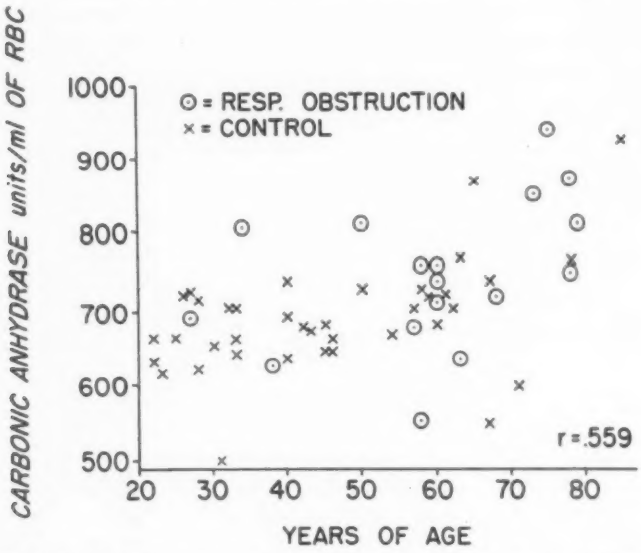

Fig. 1.—Carbonic anhydrase in units per ml. of red blood cells compared with age.

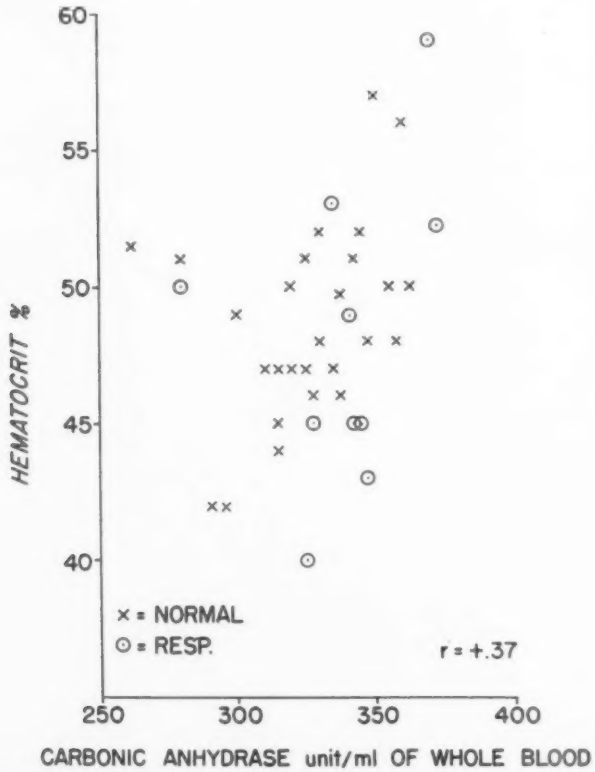

Fig. 2.—Hematocrit compared with units of carbonic anhydrase per ml. of whole blood.

blood carbonic anhydrase with increasing hematocrit ($r = +.37$, $p<.01$).

Discussion. There are 3 sets of data which need analysis and comment: the age of the patients, the carbonic anhydrase values per ml. of whole blood, and the hematocrits. Because the carbonic anhydrase in the circulating blood is located only in the red blood cell it is helpful to correct the findings to carbonic anhydrase per ml. of red blood cells. There was no difference between the respiratory group and the "normal" hospital group either in enzyme values per ml. of whole blood or ml. of red blood cell. Accordingly the two groups are fused.

The increase in age was associated with an increase in carbonic anhydrase per ml. of red blood cells. The r value was +.559 which is significant ($p<.001$). Associated with this finding there was a slight drop in the hematocrit with increasing age ($r = -.478$). However the units of carbonic anhydrase per ml. of red blood cells increase with decreasing hematocrit and this may explain in part the increase with age.

When the hematocrit is plotted against carbonic anhydrase per ml. of whole blood there is some correlation ($r = +.37$, $p<.01$) (see Fig. 2). When the units are corrected for hematocrit and expressed as carbonic anhydrase content of 1 ml. of red blood cells (Fig. 3) there is a more significant negative correlation ($r = -.65$, $p<.001$). In other words, when the amount of red blood cell mass is reduced the content of carbonic anhydrase increases. This is thought-provoking because it has been estimated that the content of carbonic anhydrase is 1000 times more than necessary for pulmonary expiration of CO_2 (Roughton[8]). Other areas of transport such as the peripheral tissue or liver may

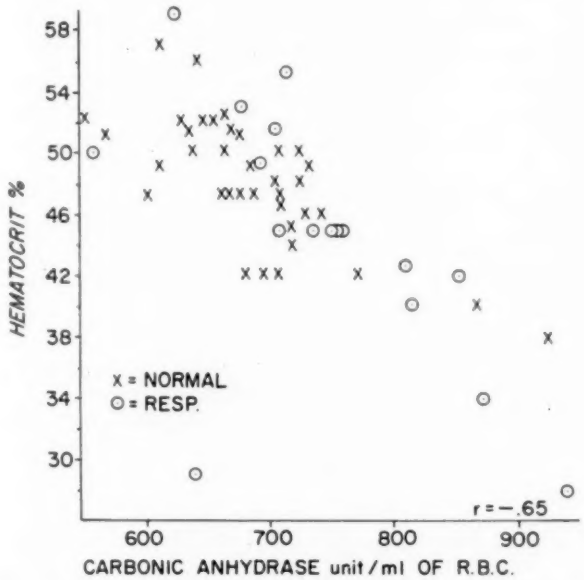

Fig. 3.—Hematocrit compared with units of carbonic anhydrase per ml. of red blood cells.

control the content of enzyme. Adams and Hansen[1] have reported that blood carbonic anhydrase in cyanotic congenital heart disease is increased proportional to the increase in hematocrit. Jamardo and Burghardt[3] found no change in blood enzyme content in patients with tuberculosis. Lambie[5] has stated that the red blood cell activity increases in proportion to the red blood cell volume. In the present study the red blood cell volume could not be estimated because red blood cell counts were not done. Lambie's hypothesis would explain the finding of elevated values in pernicious anemia and during repair of hemorrhage but it does not account for the relatively low levels found in newborns whose red blood cells are also relatively large (Adams and Hansen[1], Day and Franklin[2], and Stevenson[9]). Newborn levels by this method were found to be one-third to one-half of the adult levels.

Summary. 1. There is no significant increase in the red blood cell carbonic anhydrase activity of patients with chronic respiratory disease.

2. There was no significant correlation of carbonic anhydrase with severity of disease or serum CO_2-combining power.

3. The enzyme increases with age if the values are expressed as units per ml. of red blood cells.

4. The amount of enzyme per ml. of red blood cells decreases with increase in the hematocrit.

ACKNOWLEDGMENTS: The author wishes to thank Dr. Belding H. Scribner for access to the clinical material and Miss Verna Becker for determination of the hematocrits. Drs. Frederic C. Moll, Richard Jarvis, Blair M. Bennett, Ted Tjossem and Edwin G. Krebs assisted by criticism of the manuscript. Dr. James Sidbury gave valuable advice concerning the enzymatic determination.

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SUMMARIO IN INTERLINGUA

Activitate de Anhydrase Carbonic in le Sanguine de Patientes con Chronic Morbo Respiratori

1. In le erythrocytos de patientes con chronic morbo respiratori il non occurre un augmento significative del activitate de anhydrase carbonic.

2. Nulle correlation significative esseva notate inter le anhydrase carbonic e le severitate del morbo o le potentia del sero de combinar CO_2.

3. Le enzyma se augmento con le etate del patiente si le valores es exprimite in unitates per ml de erythrocytos.

4. Le quantitate del enzyma per ml de erythrocytos se reduce con le augmento del valores de hematocrite.

THE ANGIOCARDIOGRAPHIC PATTERNS OF INTERATRIAL SEPTAL DEFECT WITH LEFT TO RIGHT FLOW*

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Angiocardiography has rarely been used in persons with cardiac septal defect with left to right flow because of the prevalent belief that this technique is incapable of visualizing such anomalies. We have recently reported that it is possible by angiocardiography to demonstrate interventricular septal defect with left to right shunt[8]. This defect produces a pathognomonic angiocardiographic pattern. We report herein the angiocardiographic findings and pathognomonic patterns of interatrial septal defects with left to right shunt. Anatomically, these defects are customarily divided into the ostium secundum type and the ostium primum type. These two types are also physiologically different as is indicated by two distinct angiocardiographic patterns. So far as we are aware, an interatrial septal defect of the ostium primum type has not been previously recognized by venous angiocardiography.

Case Reports. INTERATRIAL SEPTAL DEFECT OF THE OSTIUM SECUNDUM TYPE. L.J., a 21-year-old female, had slowly progressive shortness of breath and fatigue over a 2-year period until walking several city blocks or one flight of steps was poorly tolerated.

She was frail and underweight. Examination was otherwise negative except for the heart. The point of maximal impulse was barely palpable in the fifth intercostal space at the left midclavicular line. A precordial systolic murmur, grade 3, was present and best heard in the left third intercostal space parasternally. P_2 was loud and reduplicated.

Conventional roentgenologic studies revealed no increase in the over-all size of the cardiac silhouette. The right ventricular outflow tract appeared enlarged. The pulmonary artery and its branches were prominent and pulsatile.

The electrocardiogram showed rightward deviation of the QRS vector and incomplete right bundle branch block. The P vector was directed 65° anteriorly. The P wave in lead 2 was 2 mm. in amplitude.

Cardiac catheterization disclosed an increased oxygen content in the right atrium. The blood oxygen content (in volumes %) was 15.1 in the superior vena cava, 17.1 in the right atrium, 18.0 in the right ventricle and 17.6 in the pulmonary artery. The pressure (in mm. Hg) was 0 (mean) in the pulmonary "capillary," 24/0 in the pulmonary artery, 35/2 in the right ventricle and 0 (mean) in the right atrium.

Angiocardiography was done immediately after cardiac catheterization. The degree and duration of opacification of the great vessels and cardiac chambers are shown graphically in Fig. 1. It is to be noted that, although the intracardiac circulation time is normal (6.3 seconds), there is marked prolongation of opacification of the cardiac chambers, pulmonary artery and aorta.

The superior vena cava is opacified for 2.8 seconds. At first, the right atrium is intensely opacified. This opacification begins to decrease at 2.8 seconds, because of mixing with non-opacified left atrial blood, and is barely visible

*Supported in part by a grant from the Heart Association of Southeastern Pennsylvania.

at 4.2 and 4.9 seconds. At 5.6 seconds, there is abrupt re-opacification of the right atrium immediately after left atrial opacification. The left atrium is never intensely opacified because of the rapid passage of opacified blood into the right atrium and left ventricle. Opacification of the right atrium gradually fades but remains visible to the end of the study because of recirculation. For this reason, the distal chambers and vessels also remain opacified for a long time.

The superior vena cava and cardiac chambers are not appreciably enlarged. The left atrial volume is 105 ml. The pulmonary artecavae is a linear zone of decreased opacification presumably representative of a thickened crista terminalis.

The middle pair of angiocardiograms was obtained at 3.5 seconds. The right atrium is barely opacified even though there is intense reflux opacification of the hepatic veins. The right ventricle is opacified but less so than previously.

The final pair of angiocardiograms was obtained at 7.7 seconds. The right atrium is again opacified, now by opacified left atrial blood. Opacification of the entire heart is not intense, however, because of re-circulation.

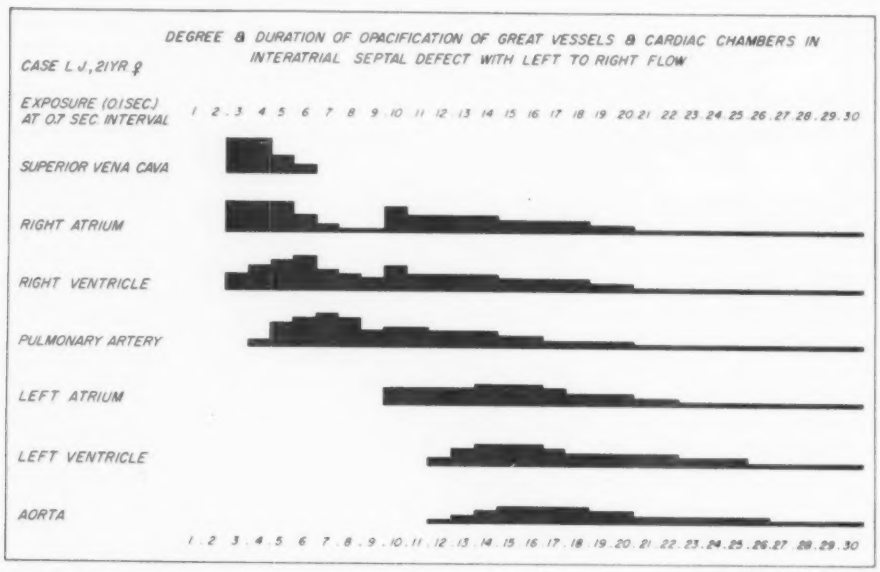
DEGREE & DURATION OF OPACIFICATION OF GREAT VESSELS & CARDIAC CHAMBERS IN INTERATRIAL SEPTAL DEFECT WITH LEFT TO RIGHT FLOW
CASE L.J., 21YR. ♀
EXPOSURE (0.1 SEC.) AT 0.7 SEC. INTERVAL
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
SUPERIOR VENA CAVA
RIGHT ATRIUM
RIGHT VENTRICLE
PULMONARY ARTERY
LEFT ATRIUM
LEFT VENTRICLE
AORTA
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

Fig. 1.—Graphic representation of angiocardiographic findings in interatrial septal defect of ostium secundum type with left to right flow. (Case L.J.)

rial branches are prominent. The inferior vena cava and the hepatic veins are enlarged, perhaps due to shunting of blood from the left atrium into the right atrium and thence into these veins.

Selected angiocardiograms and a diagram of the heart and great vessels reconstructed from sequential angiocardiograms are shown in Fig. 2. The first pair of angiocardiograms was obtained at 2.1 seconds after initial opacification of the superior vena cava. The posterior superior region of the right atrium, at the level of the orifice of the superior vena cava, shows a radiolucent defect due to non-opacified blood from the left atrium. Immediately anterior to the orifices of the venae

At surgery, a large interatrial septal defect, the size of a silver dollar, was found. A small amount of septal tissue was found extending upward from the top of the interventricular septum in half-moon fashion anteriorly and posteriorly. Similar findings were present superiorly. The pulmonary veins emptied in a normal manner.

The atrial septal defect was closed by external suturing and ligation. The postoperative course was uneventful.

INTERATRIAL SEPTAL DEFECT OF THE OSTIUM PRIMUM TYPE. C.N., a 40-year-old woman, was first recognized to have congenital heart disease at the age of 34, when she began to experience recurrent attacks of dizziness,

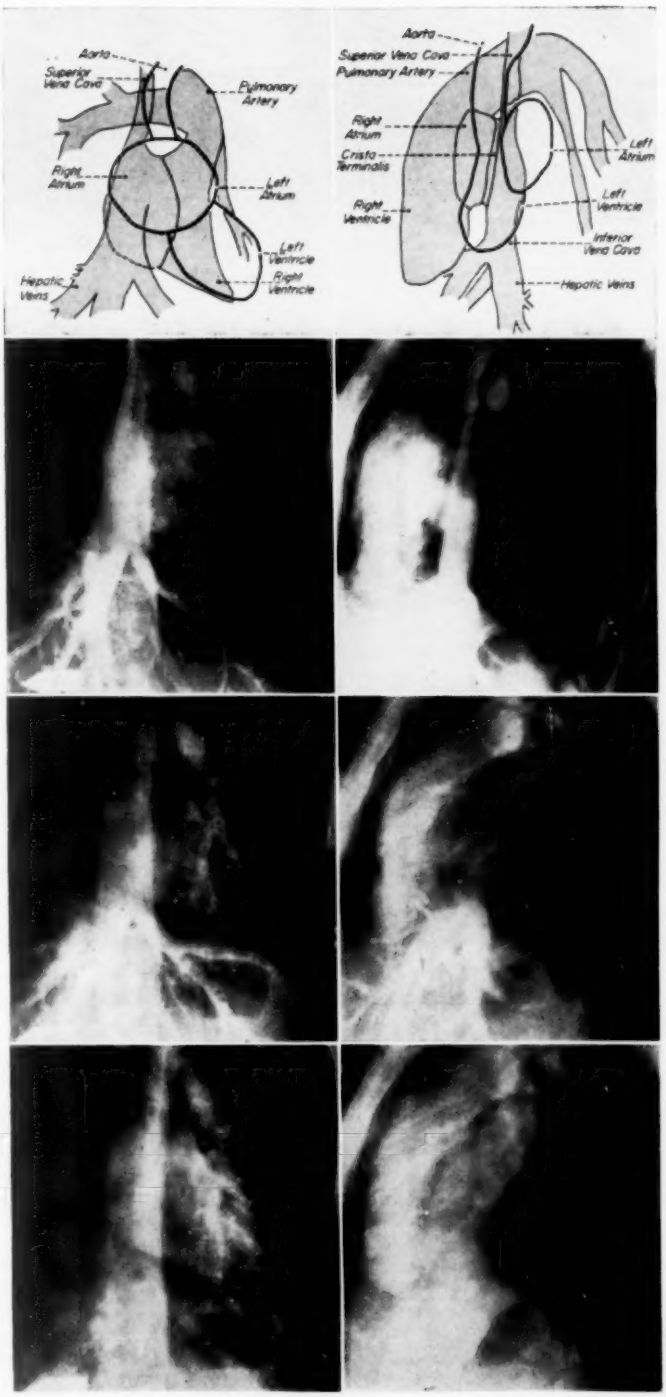

Fig. 2.—Diagram of the heart reconstructed from the sequential angiocardiograms. (Case L.J.) Simultaneous posterior-anterior and left lateral angiocardiograms at 2.1, 3.5 and 7.7 seconds. The diagram of the heart may be superimposed upon each of the angiocardiograms to aid in the recognition of the anatomic area of opacification.

weakness, palpitation and shortness of breath.

She was frail but not in acute distress. The point of maximal impulse was barely palpable in the fifth intercostal space at the left midclavicular line. M_1 was loud and split. P_2 was re-duplicated but not loud. A precordial systolic murmur, loudest (grade 2) at the apex, was audible.

Conventional roentgenologic studies disclosed a moderate increase in size of the cardiac silhouette. The aortic knob was small. The pulmonary artery and its branches were prominent. There was rounding of the left lower border of the cardiac silhouette and upward displacement of the cardiac apex.

98/10, and in the pulmonary artery, 92/44.

At surgery, a large interatrial septal defect was found. A sharp-edged lip of tissue was felt superiorly and extended anteriorly and posteriorly. Inferiorly, the defect continued down to the chordae tendineae of the tricuspid valve. The pulmonary veins emptied in a normal manner.

The defect was too large to repair. Postoperatively, the findings were unchanged but the patient was free of symptoms.

Angiocardiographic study was done on March 28, 1956. The degree and duration of opacification of the great vessels and cardiac chambers are shown graphically in Fig. 3.

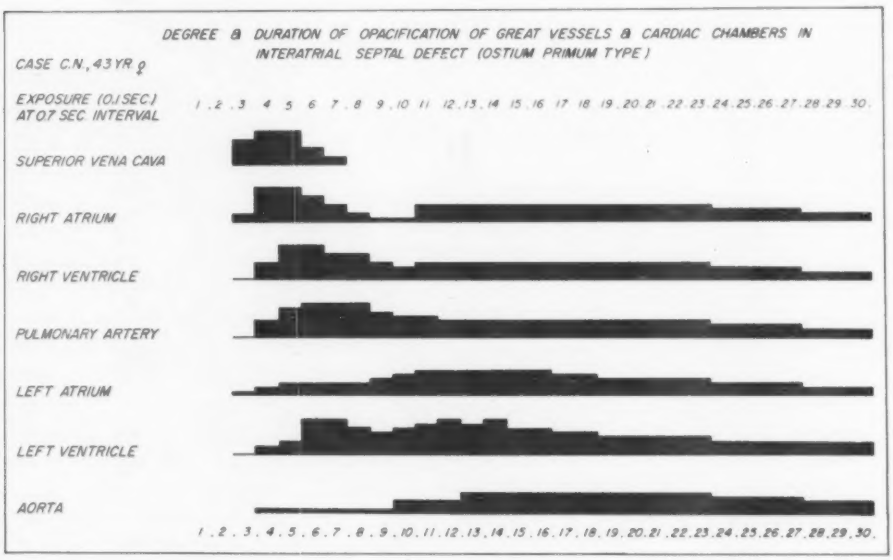
DEGREE & DURATION OF OPACIFICATION OF GREAT VESSELS & CARDIAC CHAMBERS IN INTERATRIAL SEPTAL DEFECT (OSTIUM PRIMUM TYPE)
CASE C.N., 43 YR ♀
EXPOSURE (0.1 SEC.) AT 0.7 SEC. INTERVAL
1 . 2 . 3 4 5 6 7 . 8 9 . 10 11 12 . 13 . 14 15 . 16 17 18 19 . 20 21 . 22 . 23 . 24 . 25 . 26 . 27 . 28 . 29 . 30 .
SUPERIOR VENA CAVA
RIGHT ATRIUM
RIGHT VENTRICLE
PULMONARY ARTERY
LEFT ATRIUM
LEFT VENTRICLE
AORTA
1 . 2 . 3 . 4 . 5 . 6 . 7 . 8 . 9 . 10 . 11 . 12 . 13 . 14 . 15 . 16 . 17 . 18 . 19 . 20 . 21 . 22 . 23 . 24 . 25 . 26 . 27 . 28 . 29 . 30 .

Fig. 3.—Graphic representation of angiocardiographic findings in interatrial septal defect of ostium primum type. (Case C.N.)

Analysis of the electrocardiogram showed a P vector of 70° anteriorly and a QRS vector 90° anteriorly. The QRS interval was 0.10 sec. R_1 was prominent. ST–T was depressed and T inverted in the left precordial leads.

Cardiac catheterization was done on November 13, 1952. The blood oxygen content (in volumes %) was 11.2 in the superior vena cava, 13.8 in the middle right atrium, 14.6 in the lower right atrium, 15.2 in the right ventricle and 15.2 in the right pulmonary artery. The oxygen content of blood from the femoral artery was 18.2 volumes % and its capacity 19.9 volumes %, (91.5% saturated). The pressure (in mm. Hg) in the superior vena cava was 2 (mean), in the right ventricle,

It is to be noted that, although the duration of opacification of all the cardiac chambers and of the pulmonary artery and aorta are greatly prolonged, the intracardiac circulation time is very rapid (0.7 second). This exceedingly short time is clearly due to shunting of opacified blood from the right atrium into the left ventricle. There is also immediate appearance of opacity in the left atrium indicative of a right to left atrial shunt.

The right atrium is initially intensely opacified. Its opacification decreases at 2.8 seconds and is barely visible at 4.9 and 5.6 seconds. At 6.3 seconds, abrupt reopacification of the right atrium is seen simultaneously with increased opacification of the left atrium.

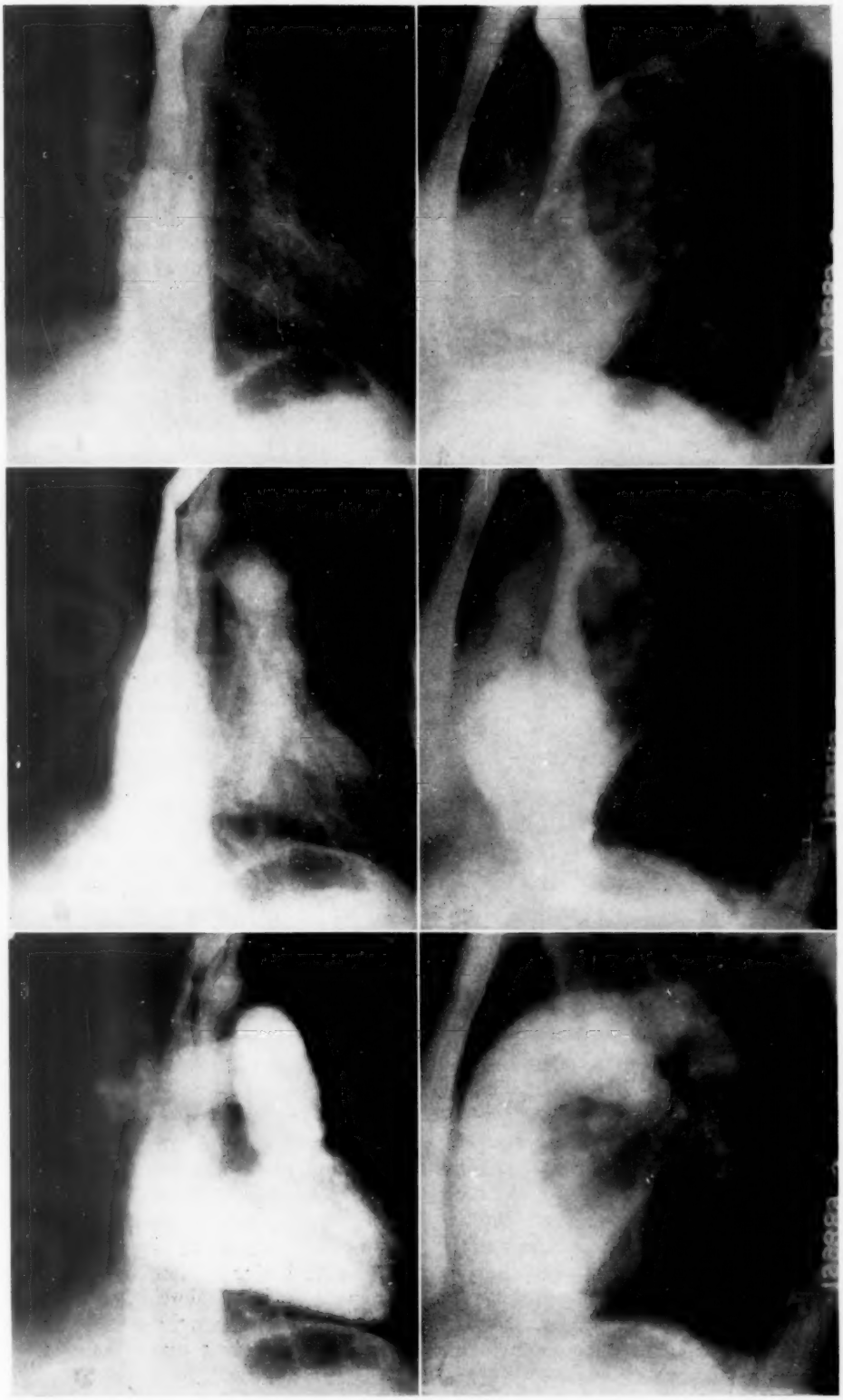

Fig. 4.—Simultaneous posterior-anterior and left lateral angiocardiograms initially and at 2.1 and 2.8 seconds. (Case C.N.)

The first films taken, represented by the first pair of angiocardiograms in Fig. 4, demonstrate the initial right to left shunt. A tongue-like projection of contrast substance extended from the inferior region of the right atrium into the inferior region of the left atrium. The middle pair, taken at 2.1 seconds, shows a barely opacified left atrium. The final pair in Fig. 4, taken at 2.8 seconds, shows intense opacification of the left ventricle. The left atrium remains barely opacified. These findings point to the right atrium as the origin of the initial opacification of the left ventricle.

A left to right atrial shunt is seen together with the right to left shunt. The first pair of angiocardiograms in Fig. 4 shows a mixing defect in the right atrium. The middle pair reveals intense, homogeneous opacification of the right atrium. The first pair of angiocardiograms in Fig. 5, taken at 4.2 seconds, shows a barely opacified right atrium. Reopacification of the right atrium is seen in the final pair of angiocardiograms in Fig. 5, taken at 7.7 seconds. This figure also contains a diagram of the heart reconstructed from the sequential angiocardiograms.

The right atrium and ventricle are slightly enlarged. The pulmonary artery and its branches are prominent. The left atrial volume is 104 ml. The left ventricular cavity is larger than normal.

Discussion. Re-opacification of the right atrium immediately after opacification of the left atrium is the pathognomonic angiocardiographic sign of an interatrial septal defect with left to right flow. One can, however, be certain that the re-opacification of the right atrium is derived from the opacified left atrium only if vessels proximal to the left atrium are not opacified or only slightly so. These vessels are the venae cavae and rarely anomalous pulmonary veins. Anomalous pulmonary veins are readily recognized by angiocardiography as is the time relationship between their opacification and that of the right atrium. On the other hand, if intense opacification of the venae cavae persists until the left atrium is opacified, re-opacification of the right atrium may not be recognizable. Such an event is common in infants and children who have extremely rapid circulation times, but is rare in adults whose circulation times are much slower. In the absence of heart failure, opacification of the superior vena cava in the adult rarely lasts longer than 2.8 seconds.

Re-opacification of the right atrium is best demonstrated in the lateral projection which maximally separates the atria. The posterior-anterior projection is necessary to exclude change in opacity due to depth alone. It also helps to identify the anatomic region of opacification. Finally, the region and intensity of opacification are most clearly recognized by comparing each film with a composite diagram of the heart reconstructed from the sequential angiocardiograms.

The presence of an interatrial septal defect may also be suspected when transient inconstant filling defects of variable extent are present in the right atrium. In the normal, with our technique, opacification of the right atrium is homogeneous and the posterior border of the right atrium in the lateral projection is smooth and sharply defined. In the presence of an interatrial septal defect with left to right flow, this border may become hazy and incomplete; and, with right to left flow, contrast substance may project from this border to a varying degree into the left atrium. Also, with left to right flow, the right atrium itself may be sparsely opacified before it becomes homogeneously opacified.

These regions of inhomogeneous opacification have been described by others and have been designated mixing defects (Figley *et al.*[3]). The spattering of opacity has been attributed to incomplete mixing of opacified and nonopacified blood. Their detection is extremely useful in alerting one to the possibility of left to right shunts. Their presence, depending upon their loca-

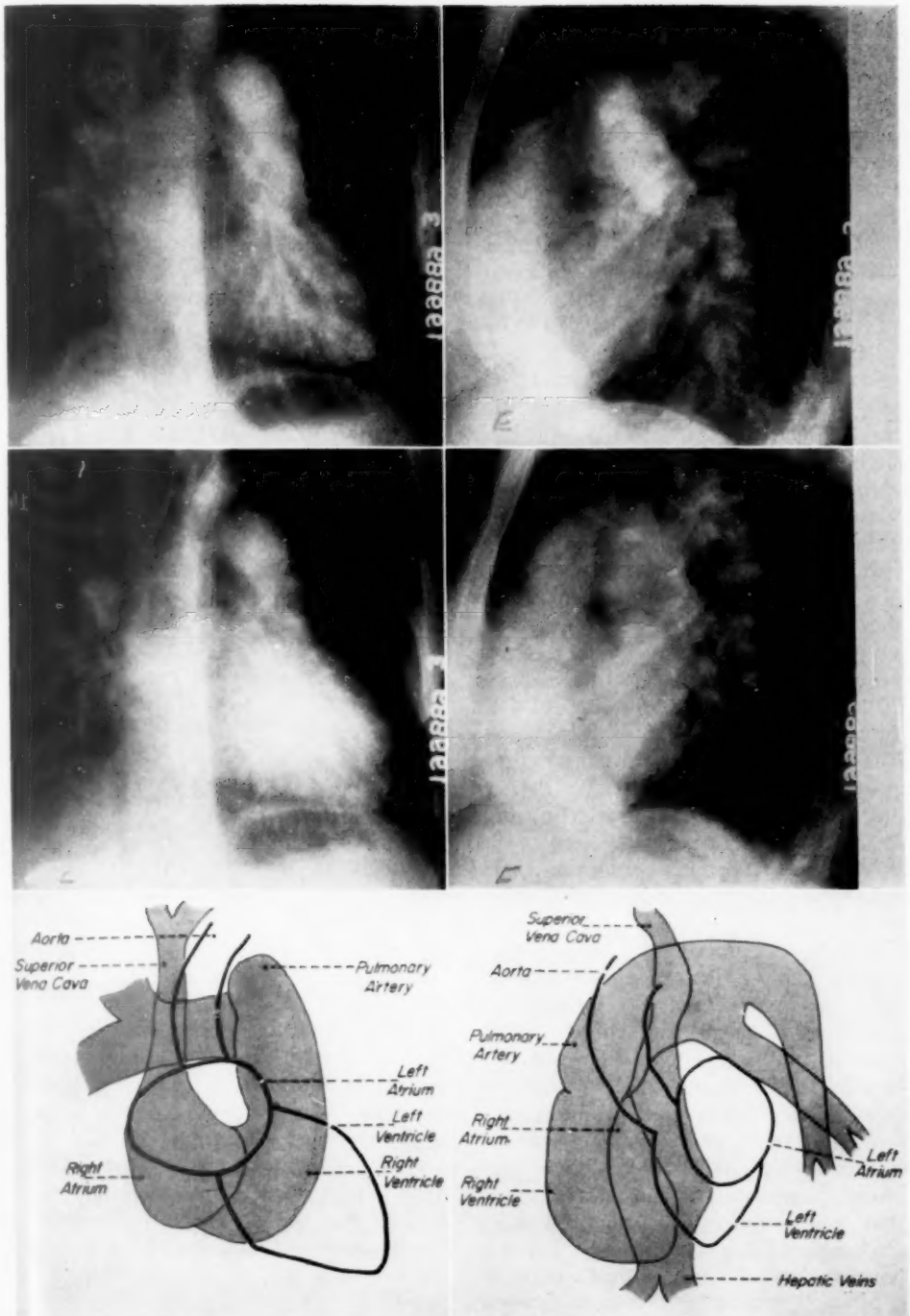

Fig. 5.—Simultaneous posterior-anterior and left lateral angiocardiograms at 4.2 and 7.7 seconds. (Case C.N.) Also, diagram of the heart reconstructed from the sequential angiocardiograms.

tion, suggests abnormal shunts between the aorta and either the pulmonary artery or heart or between the various chambers of the heart (Figley *et al.*[3], Goetz[4], Kjellberg *et al.*[5], and Lind, Spencer, and Wegelius[6]).

Mixing defects indicative of interatrial septal defects were present in our cases. They are, however, not always present. Figley and his associates found such mixing defects in only 3 of 13 persons with uncomplicated interatrial left to right shunts. It is possible that their incidence would have been higher had they used two projections rather than one, particularly the frontal plane alone which is not the most favorable projection for visualizing this defect. A shorter time of exposure of each film, as suggested by Dotter[2], may also increase the yield. On the other hand, very short exposure times may uncover normal inhomogeneous opacification which we have seen in films taken with 64 frames per second. For this reason, difficulty in interpreting mixing defects arises. Although these mixing defects are extremely valuable in alerting one to the possibility of an interatrial septal defect, we have not relied upon them alone for our angiocardiographic diagnosis.

Another characteristic angiocardiographic sign of this defect is prolongation of opacification of vessels or chambers distal to the shunt (Lind, Spencer and Wegelius[7]). This finding by itself is not diagnostic, for conditions other than shunts can produce prolongation of opacification of specific chambers or vessels. We have previously emphasized the many factors that can contribute to such findings (Soloff, Zatuchni, Stauffer and Kelly[9]). Nevertheless, a short or normal intracardiac circulation time, associated with prolongation of the right atrial time, should immediately alert the physician to the possibility of the presence of an interatrial septal defect.

In an interatrial septal defect of the ostium primum type, an additional diagnostic finding is present. In this lesion, the left ventricle becomes opacified immediately after opacification of the right atrium. This abnormal flow localizes the defect to the most inferior portion of the atrial septum. This abnormal flow is also probably a significant factor in the production of both left ventricular enlargement and systemic arterial oxygen unsaturation which were reported by Blount and his associates[1] in 2 of 5 persons with interatrial septal defect of the ostium primum type. Arterial oxygen unsaturation may also be due to right to left interatrial flow as visualized at least under the conditions of angiocardiography. Unlike the cases of Blount and his associates[1], mitral insufficiency was not present in our patient. The left atrial volume was not great nor did it vary in size. Moreover, opacity of the left ventricle, although intense, remained markedly disproportionate to the sparse opacification of the left atrium.

Summary. 1. The angiocardiographic diagnosis of interatrial septal defect with left to right flow is possible.

2. Re-opacification of the right atrium immediately after left atrial opacification is the pathognomonic finding in this lesion.

3. Transient inconstant inhomogenous opacification of the right atrium particularly posteriorly is frequently present prior to homogeneous opacification of this chamber.

4. A normal intracardiac circulation time coupled with prolongation of opacification of vessels and chambers distal to the suspected shunt is strongly suggestive of the actual presence of a shunt.

5. If, in addition to the above findings, the left ventricle is opacified immediately after the right atrium, the interatrial septal defect is the ostium

primum type. Finally, with such defects, right to left interatrial flow may also be visualized at the inferior portion of the atria.

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SUMMARIO IN INTERLINGUA

Configuration Angiocardiographic in Defecto del Septo Interatrial con Fluxo ab le Sinistra Verso le Dextera

1. Le diagnose angiocardiographic de defecto del septo interatrial con fluxo ab le sinistra verso le dextera es possibile.

2. Re-opacification del atrio dextere immediatemente post le opacification del atrio sinistre es le observation pathognomonic in iste lesion.

3. Opacification transiente, inconstante, e inhomogenee in le atrio dextere, specialmente de location posterior, es frequentemente presente ante le opacification homogenee de iste camera.

4. Un normal tempore de circulation intracardiac in association con un prolongate opacification de vasos e cameras distal al loco del suspicite derivation representa un forte indicio pro le presentia del derivation.

5. Si, a parte le supra-mentionate constatationes, le ventriculo sinistre es opacificate immediatemente post le atrio dextere, le defecto del septo interatrial es un persistente ostio prime. Finalmente, in le presentia de defectos de iste typo, le fluxo interatrial sinistro-dextere pote etiam esser visualisate al portion inferior del atrios.

EFFECT OF ACETAZOLEAMIDE (DIAMOX) ON THE ELECTROLYTE PATTERNS OF AMBULATORY PATIENTS WITH MILD CONGESTIVE FAILURE*

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The initial exhibition of Diamox (acetazoleamide) is followed in most patients by an increased rate of excretion of Na, K, and bicarbonate (Freedberg *et al.*[2]). Patients in uremia (Kaye[3]) and severely ill patients with congestive failure (Relman, Leaf and Schwartz[5]) have a minimal response. The major question that needs to be answered is its place in the therapy of patients with milder degrees of congestive failure.

In these patients the problem requiring elucidation is whether the drug will remain an efficient diuretic during prolonged medication, or whether the metabolic alterations that it produces will be adequate to block continued diuretic action.

To obtain data on this point, we have followed the serum electrolytes of ambulatory patients with mild congestive failure during therapy with Diamox (acetazoleamide).

Methods. Fourteen patients with congestive failure of diverse etiology from the Adult Cardiac Clinic of the Medical College of Virginia were chosen for study. None were thought to have cor pulmonale. All were considered fully digitalized and were on, and presumably following, a 1-gm. salt diet. All had been considered by the attending physician severe enough to receive 2 ml. of a mercurial diuretic once, or in some cases twice, a week, which was discontinued at the onset of the study. Four of the patients had a trace of pre-tibial edema at that time, and the remainder were considered edema-free. Four subjects were receiving NH_4Cl, 1 gm. q.i.d. for 3 to 4 days each week. This was discontinued 2 weeeks prior to the study. Venous blood was collected without stasis for serum Na, K, Cl and CO_2 concentration. pH was determined on arterial blood. These determinations were repeated on the 7th and 28th day of therapy. Acetazoleamide 250 mg. q.d., taken prior to breakfast, was started after the first determinations were taken and continued throughout the period of study. The following methods of analysis were used: a) Arterial pH was done utilizing the Cambridge pH Meter Model R; b) Na and K were done on the Barclay Flame Photometer; c) Chlorides were recovered by the titrometric method of Schales and Schales; d) CO_2 (content) by titration with HCl. The statistical significance of the data was calculated by analysis of variance.

Results. The plasma electrolytes measured are noted in Figs. 1 to 5. There was no significant change in sodium or potassium. There was a significant drop in CO_2 content from 29.3 mEq./L. control to 25.3 mEq./L. at

*Supported in part by a Grant from Lederle Laboratories.

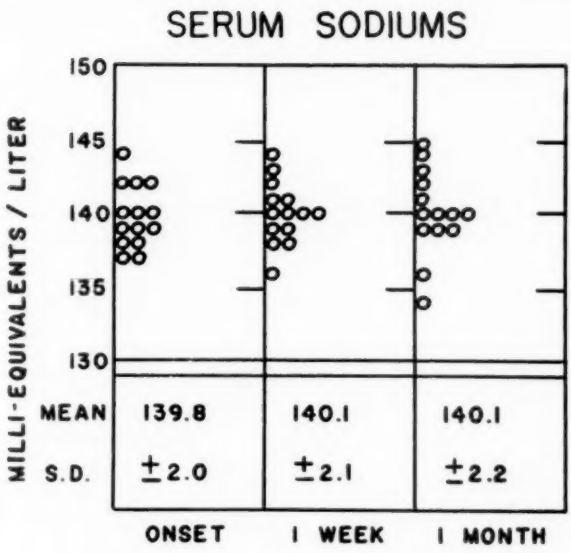
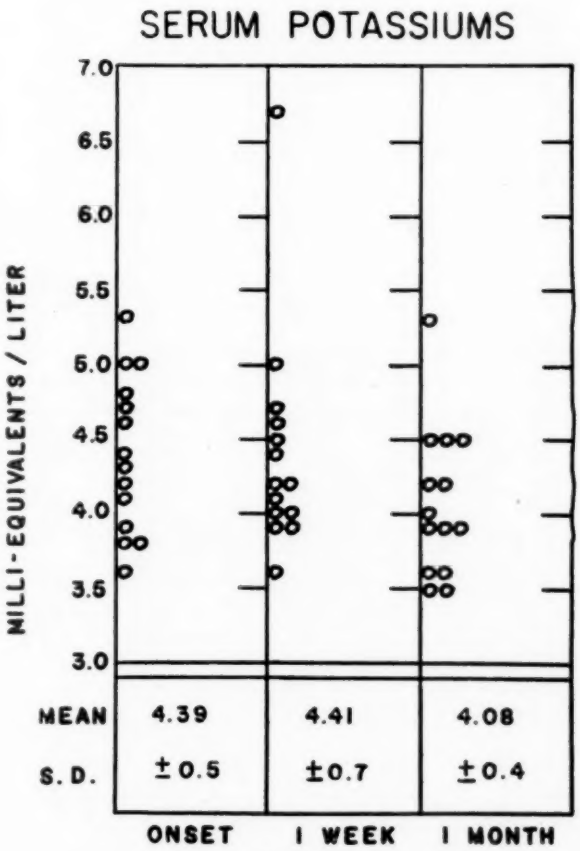

SERUM SODIUMS
MILLI-EQUIVALENTS / LITER
150
145
140
135
130
MEAN
S.D.
139.8
±2.0
140.1
±2.1
140.1
±2.2
ONSET
1 WEEK
1 MONTH

Fig. 1


SERUM POTASSIUMS
MILLI-EQUIVALENTS / LITER
7.0
6.5
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5.0
4.5
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3.5
3.0
MEAN
S.D.
4.39
±0.5
4.41
±0.7
4.08
±0.4
ONSET
1 WEEK
1 MONTH

Fig. 2

one month ($p<.01$), in arterial pH from 7.40 to 7.38 ($p>.01<.05$), and a significant increase in serum Cl from 101.2 to 104.7 ($p>.01<.05$). The results at one week were not significantly different from these at one month for any parameter. Weight did not change significantly during the month of study.

Discussion. The observed changes in electrolytes are of interest from several

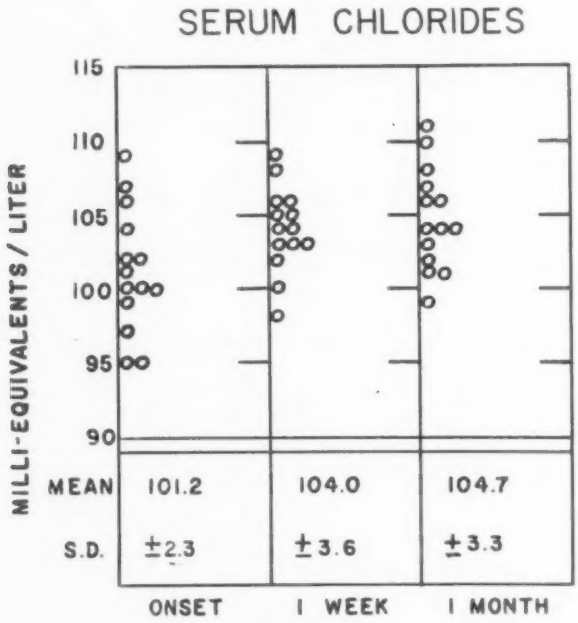

Fig. 3

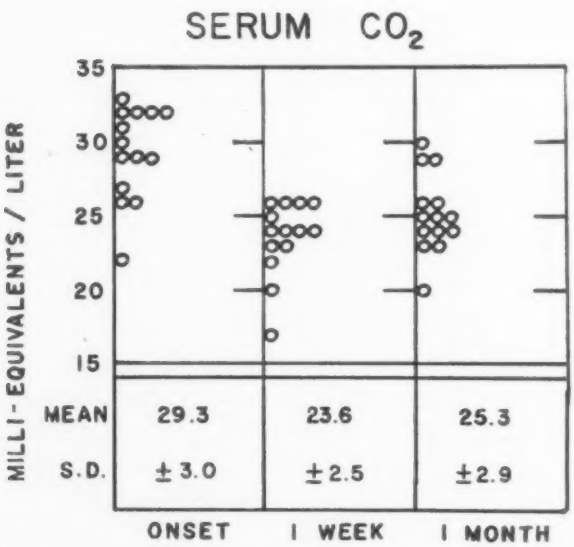

Fig. 4

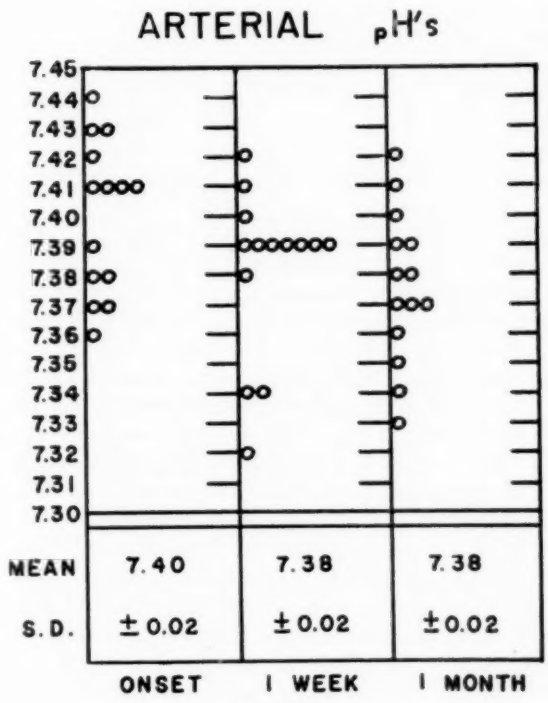

Fig. 5

Figs. 1 to 5.—Serum electrolytes prior to, and at, 7 and 28 days of therapy with 250 mg. acetazoleamide daily.

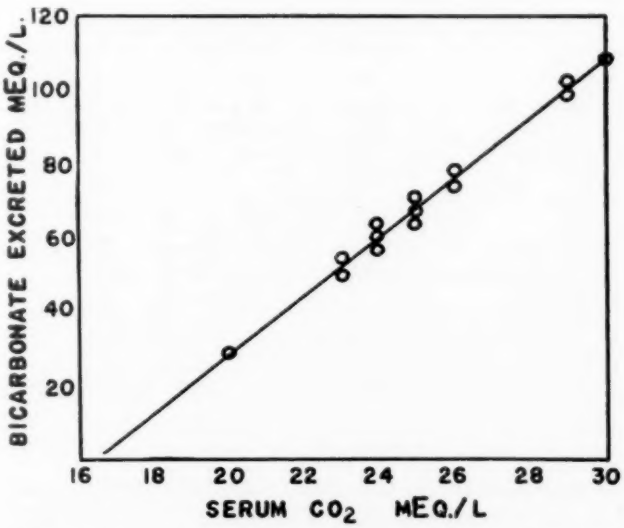

Fig. 6.—Serum CO_2 at one month of acetazoleamide therapy plotted on the regression line obtained by Counihan, Evans and Milne[1] for bicarbonate excretion during ammonium chloride acidosis.

aspects. First, does this minimal metabolic acidosis have any physiological price to the patient? This cannot be answered with certainty except to note that no untoward symptoms were observed. Secondly, is the observed bicarbonate depletion and acidosis enough to block the diuretic actions of acetazoleamide? Maren *et al.*[4] have suggested that failure to obtain the renal response to acetazoleamide is correlated with the degree of acidosis. They felt this was best measured in terms of total base depletion rather than pH. As we did not measure this, our figures cannot be directly interpolated to his. Also, though the pH changes are statistically significant, they are so small that it is difficult to feel that they are important, and we feel that it is unlikely that enough base depletion to block the renal effect of Diamox was present. The study of Counihan, Evans and Milne[1] does provide information that may be used for the interpretation of our figures. They showed that the bicarbonate diuresis produced by 250 mg. acetazoleamide was related in a linear fashion to the plasma bicarbonate level. Figure 6 shows our final bicarbonate levels, plotted on their graph of this data, the line being their calculated regression line for NH_4Cl acidosis. All values save one fall within limits allowing appreciable diuresis. If this reasoning is valid, it would seem that our patients at 28 days still maintained a plasma bicarbonate level that allowed considerable bicarbonate diuresis upon acetazoleamide exhibition. The maintenance of normal K levels cannot prove the absence of depletion of total body K, but provides no suggestion that this had occurred.

The absence of weight gain in our patients after discontinuing mercurial diuretics could be used as evidence for the value of this drug in controlling congestive failure. This may be true, but we do not put this interpretation upon our data, as we do not know what their course would have been without therapy.

Summary and Conclusions. Acetazoleamide, 250 mg. daily, causes a statistically significant drop in serum CO_2 content and arterial pH at 7 and 28 days. A significant rise occurs in Cl. No significant change occurs in serum Na and K. It is suggested that the observed changes are inadequate to nullify its diuretic action.

ACKNOWLEDGMENTS: We wish to thank Dr. Murray Mitts for statistical analysis of the results, Dr. T. H. Maren for advice, Drs. Nelson Young and J. H. Patterson for laboratory aid, and Drs. W. B. Porter and P. D. Camp for access to patients.

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SUMMARIO IN INTERLINGUA

Effecto de Acetazoleamido (Diamox) Super le Electrolytos de Patientes Ambulatori con Leve Disfallimento Congestive

Acetazoleamido in doses diurne de 250 mg causa un statisticamente significative reduction del contento seral de CO_2 e del pH arterial post 7 e 28 dies. Un

augmento significative occurre in Cl. Nulle alteration significative occurre in le Na e le K del sero. Nos opina que le alterationes observate non suffice a annullar le action diuretic del droga.

SUMMARIO IN INTERLINGUA

(See page 145 for original article)

Le Rar Occurrentia de Carcinoma Metastatic in le Hepate Cirrhotic

Le incidentia de cirrhosis del hepate variava in le duo hospitales includite in le presente reporto. Illo amontava a 3,12 e 5,74%, respectivemente, de omne necropsias executate in patientes de plus que 20 annos de etate. Le incidentia variava con etate, sexo, e racia. Le frequentia de cirrhosis esseva practicamente identic in homines e in feminas blanc, sed illo esseva plus alte in homines que in feminas negre. Le incidentia medie de cirrhosis esseva considerabilemente plus alte in le racia blanc que in le racia negre. Le proportion inter blancos e negros esseva 2:1 pro homines e circa 3:1 pro feminas.

Le incidentia de carcinoma in patientes de 20 annos o plus de etate amontava a 15,12% de omne necropsias a un hospital e a 23,2% al altere hospital. Le incidentia de carcinoma etiam variava con etate, sexo, e racia. Esseva constatate pauc differentia in le incidentia medie de carcinoma inter homines blanc e feminas blanc a ambe hospitales, e le mesme observation valeva pro homines e feminas negre. Tamen, le incidentia medie de carcinoma in masculos negre esseva circa un medietate del incidentia in masculos blanc, e in femininas negre le incidentia esseva circa duo tertios de illo in femininas blanc. Iste calculation valeva pro le un del duo hospitales ubi le numero total del casos sufficeva pro un analyse adequate. Le incidentia culminal de carcinoma occurreva circa un decennio plus tarde que le incidentia culminal de cirrhosis.

Le incidentia medie de cirrhosis del hepate in patientes qui ha carcinoma in varie sitos non incluse le hepate esseva circa un medietate del incidentia occurrente in le population necropsiate in general.

Carcinoma metastatic del hepate esseva frequente (28,6% de omne carcinomas). Tamen, carcinoma metastatic del hepate con cirrhosis portal esseva rar (0,12% de omne carcinomas). Dece-nove tal casos esseva trovate in le litteratura. A iste total le presente reporto adde 6 nove casos. Es proponite un numero de causas o factores responsabile pro iste rar occurrentia, *i.e.* le infrequente occurrentia de cirrhosis hepatic in casos de carcinoma in altere partes del corpore; le reducite superviventia in le presentia del occurrentia simultanee de ille duo morbos; alterate cambiamentos metabolic e enzymatic in le hepate; alterationes del relationes vascularcon attenuation e stenosis del brancas venose portal, producente un impedimento mechanic del usual typo de embolisation e dissemination del cancere in le hepate; e le formation de spisse trabeculas fibrose que servi a additionalmente impedir o prevenir le crescentia e le dissemination de cellulas neoplastic.

EFFECT OF ARYL SULFONYLUREA ON THE PLASMA DISAPPEARANCE OF LABELED INSULIN IN DIABETICS*

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AND

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The mechanism of action of the hypoglycemia producing sulfonylureas is not clear. Bertram, Bendfeldt and Otto[2] present evidence to show that there is a destructive effect on the alpha cells of the pancreas, thus removing the effect of the hyperglycemia producing secretion of these cells. This cannot explain the action of these compounds since no effect is produced in the alloxanized animal (Achelis and Hardebeck[1]) where presumably the alpha cells are intact.

Mirsky[6] has shown that the aryl sulfonylureas act as noncompetitive inhibitors of insulinase in liver slices and has advanced the hypothesis that insulin insufficiency in diabetes may be due to an increased rate of insulin destruction. Vaughan[8] found, however, that aryl sulfonylurea did not inhibit insulinase activity in concentrations in which it altered glucose metabolism in liver slices. The following study is designed to show the effect of aryl sulfonylurea on the plasma disappearance rate of labeled insulin in diabetic patients.

Method. The patients selected for this study were diabetics who had been managed on insulin prior to treatment with Orinase†. The studies outlined below were carried out on these patients both before and after treatment with the drug. Orinase blood levels were in the range between 5 and 15 mg. per 100 ml. after oral administration. Insulin therapy was withdrawn for 24 hours before the studies were carried out. Insulin labeled with I^{131} was prepared by the method described by Ferrebee *et al.*[5]. The studies were carried out by injecting into the fasting diabetic patients 3 units per $M.^2$ body surface of insulin-I^{131}. Blood samples were drawn at 20-minute intervals for one hour and a precipitate of the plasma prepared by treatment with zinc hydroxide. The precipitate was dissolved in 15% sodium hydroxide, made up to a constant volume, and assayed for radioactivity in the end window Geiger counter. The counts obtained were then converted to insulin concentration (microunits per ml. plasma) using the appropriate conversion factor. Urine collected at the end of one hour was dialyzed against water and the dialyzable radioactivity determined.

Results. The plasma disappearance curves for the protein bound radioactivity follow the first order law for the first 2 hours after injection. The rate constants for the logarithmic curve of disappearance shown in Table 1 are expressed as per cent. In each case there is a statistically significant increase in the plasma disappearance rate after Orinase (Fig. 1). This effect is noted regardless of the clinical re-

*Supported by Grant-in-aid from the United States Public Health Service.

†Orinase, brand of tolbutamide, supplied by the Upjohn Company through the courtesy of Dr. C. J. O'Donovan.

sponse of the patient, since the diabetes in Cases 2 and 4 could not be controlled in spite of adequate blood levels of the drug. Also there appears to be no correlation between the Orinase blood level and the magnitude of the change in the slope.

The theoretical concentration of labeled insulin at zero time is found by extrapolation of the disappearance curve. These values are shown in Table 1. In 4 of the patients, there is an increase in the zero time concentration reflecting a decrease in the "space" of

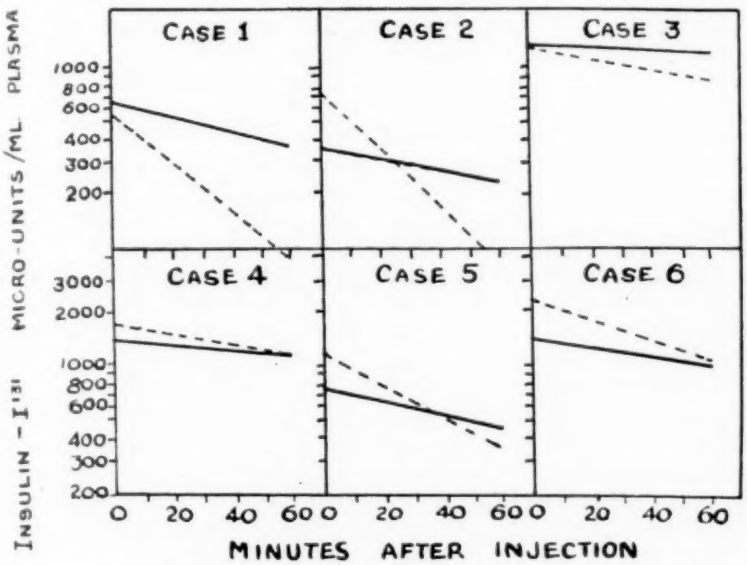

Fig. 1.—Logarithmic plot of the disappearance curves for each case before (solid line) and after (dotted line) Orinase. The lines are derived by the method of least squares for points obtained between 20 and 120 minutes after injection of labeled insulin. The difference between the slopes in each case is significant ($P<.01$).

TABLE 1.—EFFECT OF ORINASE ON PLASMA INSULIN DISTRIBUTION AND DISAPPEARANCE

Case		*Zero Time Conc. 10^{-6} Units/ml.*	*Rate Constant % Per Min.*	*Urine I^{131} % of Dose*
1	Pre*	644	0.89	2.39
	Post	566	3.06	2.30
2	Pre	375	0.73	2.61
	Post	713	3.26	0.45
3	Pre	1432	0.21	2.29
	Post	1415	0.65	1.37
4	Pre	1438	0.55	—
	Post	1605	0.73	—
5	Pre	756	0.78	5.81
	Post	1068	1.48	4.47
6	Pre	1630	0.28	2.97
	Post	2222	0.75	1.65

*Pre and post indicates before and after treatment with Orinase.

distribution for the labeled material. In one of the patients there is no change in this value and in the other an actual increase.

Discussion. The increased disappearance rates after Orinase might be interpreted to mean that insulin is being degraded more rapidly; however, there is noted no increase in the urinary excretion of radioiodine. This strongly suggests that the rate expressed by this disappearance curve is more closely related to the utilization of insulin rather than to its destruction. It is quite possible that the value for the theoretical concentration at time zero may be more closely related to the rapid destruction of insulin through an insulinase mechanism as described by Mirsky and Broh-Kahn[7]. This theoretical initial concentration of labeled insulin was increased in 4 of the above cases, consistent with the hypothesis that the initial rapid destruction of insulin had been retarded. A decreased plasma disappearance rate for labeled insulin has been noted experimentally after hepatectomy (Elgee and Williams[4]) and after nephrectomy (Bolinger and Slinker[3]). Increase in the initial concentration of labeled insulin has been noted in the rabbit after liver damage but not after nephrectomy (Bolinger and Slinker[3]). The possibility must be considered that the aryl sulfonylurea exerts its hypoglycemic effect by acting primarily on the liver where the highest concentrations of insulinase are found (Mirsky and Broh-Kahn[7]), thus protecting insulin against destruction in this organ so that it can be used in the other tissues.

Summary. The plasma concentration and disappearance rate of insulin-I^{131} has been studied in 6 diabetic patients before and after treatment with aryl sulfonylurea. In all of the patients there was a significant increase in the plasma disappearance rate after treatment. In 4 of the patients there was an increase in the theoretical initial concentration of the labeled insulin. The findings suggest that the metabolism of insulin is affected in two different ways consistent with a hypothesis that there are two pathways for the handling of insulin. The rapid phase of insulin disappearance was slowed down in 4 cases, as shown by the higher initial concentrations, while the slow phase of insulin disappearance was accelerated after treatment with the aryl sulfonylurea.

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SUMMARIO IN INTERLINGUA

Effecto de Arylo-Sulfonylurea Super le Disparition, ab le Plasma de Diabeticos de Insulina Etiquettate per I^{131}

Le concentration e le disparition de insulina a I^{131} esseva studiate in le plasma de sex diabeticos ante e post tractamento con arylo-sulfonylurea. In omn

patientes, un significative acceleration del disparition de insulina a I^{131} ab le plasma esseva notate post le tractamento. In quatro del patientes il habeva un augmento del concentration initial theoric del insulina etiquettate a I^{131}. Le constatationes suggere que le metabolismo de insulina es afficite in duo manieras differente, de accordo con le hypothese que il existe duo vias de transition pro insulina. Le phase rapide del disparition de insulina esseva relentate in quatro casos (manifeste in le plus alte concentrationes initial), durante que le phase lente del disparition de insulina esseva accelerate post le tractamento con arylo-sulfonylurea.

SUMMARIO IN INTERLINGUA

(See page 153 for original article)

Le Effectos de Analgesicos Narcotic e de Antagonistas Narcotic Super le Respiration

Le datos presentate rende evidente le sequente factos relative a patientes qui es levemente anesthesiate con thiopental e un mixtura de oxydo nitrose con oxygeno:

Tanto 2 mg/kg de Demerol (meperidina) como 0,66 mg/kg de Nisentil (alphaprodina), *i.e.* doses de approximativemente equal virtute analgesic, deprimeva marcatemente le function respiratori. Iste effecto depressori es plus profunde e plus prolongate post le administration de alphaprodina que de meperidina. Le frequentia respiratori es afficite a uniformemente plus alte grados que le volumine del aere currente, le volumine per minuta, e le mesura del ventilation alveolar.

Tanto 0,03 mg/kg de Lorfano (levallorphano) como 0,15 mg/kg de Nallina (nalorphina), administrate sin narcotico, produce leve depressiones del frequentia respiratori, del volumine per minuta, e del mesura del ventilation alveolar, 4 minutas post lor injection.

Le supra-mentionate doses de levallorphano o nalorphina, administrate 4 minutas post 2 mg/kg de meperidina o 0,66 mg/kg de alphaprodina, promptemente neutralisa le depression respiratori causate per ille analgesicos narcotic. Le effecto super le frequentia respiratori es minus pronunciate que le effecto super le altere factores studiate. Le depression inducite per meperidina es possibilemente antagonisate a un alique plus alte grado que le depression inducite per alphaprodina.

Similemente, levallorphano o nalorphina, administrate 5 minutas ante meperidina o alphaprodina, preveni le depression respiratori a un grado considerabile. De novo, iste effecto protectori del antagonistas narcotic es possibilemente alique plus pronunciate contra le depression inducite per meperidina que contra illo inducite per alphaprodina.

Finalmente, levallorphano administrate simultaneemente con meperidina in le doses studiate preveni le marcate depression respiratori producite per meperidina quando administrate sol.

ELECTROCONVULSIVE THERAPY IN PATIENTS WITH STRUCTURAL DISEASE OF THE CENTRAL NERVOUS SYSTEM

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The clinical application of electroconvulsive therapy was limited by many arbitrary contraindications when that technique was first introduced. Thus, Smith *et al.*[12] stated in 1942 that electric shock should not be used when the patient has: "(1) evidence of cerebral lesions; (2) tuberculosis, active or inactive; (3) advanced heart disease, regardless of etiology; (4) bone disease, except osteo-arthritis of moderate degree; (5) malignant tumors, active or 'cured'; (6) inanition, especially if coupled with prolonged inactivity or bed confinement; (7) thrombophlebitis, glaucoma and other conditions which in the opinion of the clinician would make drastic therapy unwise."

Increasing experience with the efficacy of this mode of treatment of severe affective disturbances led to the recognition that each patient must be considered as an individual problem, and that the relatively rigid contraindications of earlier thinking had to be considerably modified (Ehrenberg and Gullingsrud[3], Gallinek[5], Kalinowsky and Hoch[8], McKnight, Burbridge and Guth[9], Tucker, Fleming and Raeder[16], and Wolff[17]). Thus, such diseases as thrombophlebitis, glaucoma, tuberculosis, heart disease, and the like, are no longer considered as absolute deterrents to electroshock therapy, when the proper psychiatric indications are present.

Among those organic diseases which have been considered as seriously increasing the hazards of electroshock therapy, those of the central nervous system seem to have maintained a forbidding reputation. Thus, for example, Heilbrunn and Feldman[7] concluded, after observing prolonged postconvulsive cyanosis and apnea in 4 patients suffering from general paresis, that "the syphilitic brain constitutes a *locus minoris resistentiae*, prone to succumb rather readily to an exogenous force such as an electrically induced convulsion." Nonetheless, other clinicians have successfully treated patients with affective disturbances and coexistent central nervous system disease, and have not observed unusual complications (Ehrenberg and Gullingsrud[3], McKnight, Burbridge and Guth[9], Petersen[10], Savitsky and Karliner[11], Solomon, Rose and Arnot[13], and Stern[14]).

This report concerns 24 patients who had structural disease of the central nervous system, and who were treated, because of severe psychiatric disturbances, by electroshock therapy. For the purpose of discussion, these patients will be grouped according to their neurologic disorder. Six patients had intracranial neoplasms, 5 had

cerebrovascular accidents, one patient had both central nervous system syphilis and a cerebrovascular accident, 2 additional patients had central nervous system syphilis, 3 patients suffered from paralysis agitans, 3 patients had spinal cord disease, and 4 patients had severe dystonic syndromes.

The technique of treatment consisted of the intravenous administration of Thiopental Sodium, to the point where the patient no longer responded to verbal stimuli. This was followed by the bi-temporal application of a unidirectional current from a Reiter machine, to produce a grand mal seizure. Treatments were usually administered every other day.

Intracranial Neoplasm. Six patients with intracranial neoplasms were treated with electroshock therapy. The presence of the neoplasm was unknown at the time of institution of treatment.

Case Reports. CASE 1. A 60-year-old man had a recurrence of a severe suicidal depression. One year before he had been given 4 electroconvulsive treatments because of a similar depression. When he was originally treated, and again at the onset of the present depression, careful neurological examinations failed to reveal any evidence of organic disease of the nervous system. A course of electroconvulsive therapy was again started. Following the third treatment, the patient developed a severe and prolonged confusional state, which contrasted strongly with his reaction to the first course of therapy. He was then hospitalized. A frontal lobe meningioma was diagnosed and successfully removed.

CASE 2. A 39-year-old man sought treatment for severe atypical facial and neck pains. Over a 2-year period he had consulted 51 other physicians. Examination disclosed evidences of severe psychiatric disturbances: for example, depression, agitation, narcotic addiction, and the like, but none of organic diseases of the nervous system. He received 6 electroconvulsive treatments with no improvement in his original complaint. It was noted, however, that after the fourth treatment he developed a severe and persistent confusional state. Subsequently, 4 months after therapy, diagnostic studies in a hospital revealed a right sphenoidal ridge meningioma. The patient expired 24 hours after operation.

CASE 3. A 70-year-old man had a 6-month history of withdrawal, insomnia, anorexia, marked concern with bowel function, self-incriminating thoughts, frequent crying spells, and a 30-pound weight loss. Neurological studies disclosed a positive face-hand test (hand extinction) and minimal dyscalculia, but were otherwise normal. He was given 5 electroconvulsive treatments. After the third treatment he became increasingly disoriented, and showed bradyphrenia, paraphasia and perseveration of thought. His depression, however, was significantly decreased. The organic mental syndrome cleared over the succeeding 4 to 6 weeks, although it never completely disappeared. There was a return of some of the somatic preoccupation, but the patient was able to function with a minimum of supervision for the next 5 to 6 months. After this interval he showed a gradual and progressive reappearance of disorientation, followed by the onset of Jacksonian seizures. Hospitalization and further studies led to the diagnosis of a right fronto-temporal glioblastoma multiforme. The patient succumbed several days after operation.

CASE 4. A 69-year-old man was hospitalized 3 times during a 4-month period because of bizarre neurologic and psychiatric symptoms and signs. The former consisted of memory defects, trunkal ataxia, positive Romberg, dysdiadokokinesis of the left upper extremity, hyperreflexia in the lower extremities, and deficits in position sense and vibration appreciation in the lower extremities. The psychiatric disturbance was characterized by a severe agitated depression and overt suicidal ideation. When diagnostic studies did not disclose a mass lesion, he was treated with electroshock. He received 5 treatments and rapidly developed a profound, persistent organic mental syndrome, although the depressive features tended to disappear. Eleven days after the last treatment the patient had a massive intracranial hemorrhage. He subsequently recovered from this acute bleeding episode, but was left with a quadriparesis and other sequelae presumably resulting from brain stem damage. Death occurred between 2 and 3 months later. At necropsy, a glioblastoma of the corpus callosum was discovered.

CASE 5. A 47-year-old man had a generalized seizure 6 years prior to his presenting complaint of a second, right-sided seizure. He also complained of severe recurrent headaches for 1½ years. During a period of 2 to 3 months of close observation and investigation, the seizures became increasingly frequent, and

he developed a progressive weakness of the right upper extremity. This was accompanied by an increasingly severe depression syndrome. Because no mass lesion could be demonstrated, and because the depression developed into a serious threat to his life, electroconvulsive treatment was started. The depression syndrome improved slightly, but the right-sided paresis continued to progress. In addition, after the fourth treatment, he suddenly became aphasic. An exploratory craniotomy then disclosed an infiltrating glioblastoma in the left frontal lobe.

CASE 6. A 56-year-old man had several brief episodes of apparent alteration of consciousness during the month prior to the institution of electroconvulsive therapy. His private physician administered the treatments under the impression that the primary problem was one of involutional depression. Following the second treatment, the patient slept intermittently for 12 hours and on awakening was severely disoriented and had a jargon aphasia. These symptoms tended to clear during the succeeding few days but the patient was "nervous and upset" the following week. He was then hospitalized and a left temporoparietal glioblastoma was demonstrated.

Discussion. It is evident in this series, that from the viewpoint of alleviation of psychiatric disturbances, electroshock treatment was of dubious value. An exception is Case 3. This patient was partially relieved of his agitated depression for 5 to 6 months. It is also not unlikely that Case 1 obtained a year remission of his psychiatric disturbances, despite the probable presence of a meningioma, when he was first given a course of electroshock treatment. However, it seems clear that in the majority of these patients with intracranial neoplasms, electroshock therapy did not alleviate the agitation and depression. Moreover, these treatments provoked an exacerbation of organic disability.

Our experience parallels that of other clinicians. Savitsky and Karliner[11] reported the case of a woman who became stuporous after the second electroshock treatment. A right temporo-occipital glioblastoma was found at operation. Delay[2] described a 42-year-old woman whose depression was exacerbated with 6 electroshock treatments, and who subsequently was discovered to have a glioma of the left cerebrum. Gralnick[6] described the case of a 60-year-old woman who became somnolent and died 4 days after the second electroshock treatment. At necropsy a sub-frontal meningioma was discovered.

It is noteworthy that of the 6 patients with intracranial tumors, 5 developed a severe and persistent confusional state after relatively few electroshock treatments. Thus, a severe organic mental syndrome developed after the third treatment in Case 1, after the fourth treatment in Case 2, after the third treatment in Case 3, after the fifth treatment in Case 4 and after the second treatment in Case 6. Case 5 was given only 4 electroshock treatments and did not develop a confusional state. However, his right-sided weakness did increase, and after the fourth treatment, very marked aphasic difficulties appeared.

During the course of electroshock therapy of patients without structural disease of the central nervous system, mild to moderate organic mental syndromes often develop. However, these syndromes appear late in the course of treatment, are usually not severe and are transient. Furthermore, the immediate post-ictal confusional state usually shows a marked amelioration in an hour or two, even when a moderately severe organic mental syndrome has already been established in the course of treatment.

In our series, the patients with intracranial neoplasms, in marked contrast to the above, seemed to rapidly develop severe and prolonged organic mental syndromes. These syndromes appeared early in the course of treatment, and showed little or delayed

improvement between treatments. The consistency of this finding, even in such a limited series as this, is striking. It strongly suggests that alterations in cerebral physiology, imposed by the neoplasm, render brain function more susceptible to disorganization by electroconvulsive therapy.

This phenomenon has a clinical implication. It is known that intracranial neoplasms may be silent in terms of neurologic signs or symptoms, also that a tumor may precipitate a psychiatric syndrome as its first sign. It is also known, though at times overlooked, that a patient with a clearly defined functional, psychiatric disorder may have an independent, structural neurologic disease. Therefore, the rapid appearance and persistence of a severe organic mental syndrome, in a patient being treated with electroshock, for an apparently functional psychiatric disorder, should give rise to the suspicion of possible organic brain disease.

Since older patients, with diffuse vascular or degenerative disease of the brain, also tend to develop a rapid and persistent confusional state under electroshock therapy, the appearance of an early organic mental syndrome cannot in any real way be equated with the presence of an intracranial tumor. However, we believe that when this type of mental syndrome does appear in a patient who does not belong in the category of degenerative and vascular brain disease, the clinician must seriously consider the possibility of a silent intracranial neoplasm, and proceed accordingly.

Cerebrovascular Disease. Six patients who had had cerebrovascular accidents, and then developed severe affective disturbances, were treated with electroshock.

CASE 7. A 65-year-old man whose past history included cardiovascular and central nervous system syphilis, diabetes mellitus, and several episodes of congestive heart failure, suddenly developed a right hemiparesis from a cerebrovascular accident. Shortly thereafter symptoms of a severe agitated depression appeared. Nine weeks later he was started on a course of 14 electroshock treatments. The agitated depression resolved, and there was no apparent deleterious effect on his physical status. It was noted that invariably, during the induced seizure, the right or paretic upper extremity was elevated, whereas the left, or normal upper extremity was not.

CASE 8. A 34-year-old woman developed a sudden left hemiparesis and hemisensory defect, probably as a result of a thrombosis in the distribution of the right middle cerebral artery. The paresis and sensory deficit improved during the 4 weeks following the ictus. However, she manifested a bizarre mental syndrome which included monosyllabic drawling speech, paraphasic errors and a moderately severe depression. Twenty electroshock treatments were given, beginning 4 weeks after the cerebrovascular accident. This produced a marked improvement in the psychiatric illness. Her neurologic disability continued to improve. It was noted that during the induced seizure, the left lower, or paretic extremity was invariably elevated above the right extremity, and that her body twisted to the right.

CASE 9. A 43-year-old man with severe hypertension had a cerebral hemorrhage, causing a right hemiplegia and aphasic difficulties. He developed a severe depression syndrome. One year after the ictus, he was given 6 electroshock treatments. His blood pressure at that time ranged as high as 236/136. The depression cleared. There was no adverse effect upon his physical or neurologic status. It was noted that during the induced seizures, the right, or paretic extremities, were consistently elevated higher than the left, and that his body turned to the left.

CASE 10. A 63-year-old woman with marked hypertension and arteriosclerotic heart disease had a cerebrovascular accident involving the right middle cerebral artery. Because of a progressive, agitated, suicidal depression, electroshock treatment was begun about 5 months after the ictus. After 8 electroshock treatments her psychiatric disturbance had resolved without complication. It was noted that during the induced seizures the left lower, or paretic extremity, was elevated more than the right, and that her body consistently turned to the right.

CASE 11. A 55-year-old woman suffered a right cerebrovascular accident. She was a relatively severe diabetic and had had several

episodes of congestive heart failure in the past. She had also been treated for pernicious anemia for 20 years. Because of a severe agitated depression, electroshock treatment was started 6 weeks after the stroke. It was again noted that during the induced seizures, there was a greater tonus and flexion of the paretic extremities than of the normal ones. After the fifth treatment, she developed an organic mental syndrome. One week later, after this had resolved, the sixth treatment was given. Following this treatment the patient did not recover consciousness and remained in coma till death, 6 days later. Necropsy was not permitted.

CASE 12. A 48-year-old man with a past history of severe hypertension and myocardial infarction, sustained a right cerebrovascular accident. Subsequently he became depressed and complained continually of severe burning dysesthesia in the left lower extremity. Large doses of Chlorpromazine, up to 675 mg. a day, were ineffective during a 3-week trial. Three days after discontinuing the Chlorpromazine, and about 2 years after the ictus, he was given an electroshock treatment. Immediately following the grand mal seizure, respirations resumed normally, but after several minutes became shallow and ceased, as did the heart beat. Necropsy was not permitted.

Discussion. Many authors have reported successful treatment by electroshock of patients with evidence of cerebrovascular disease. These authors include Gallinek[5], Ehrenberg and Gullingsrud[3], Evans[4], Savitsky and Karliner[11], among others.

In our series of 6 patients with known cerebrovascular disease, 2 patients died following electroshock treatment. Although necropsy was not permitted and the exact mechanism of death is unknown, there seems ample reason to be suspicious that the electroshock treatment was causally related to the mortality. Whether the mode of death was through damage to cardiovascular or central nervous system function is not known.

The other 4 patients derived considerable benefit from the electroshock treatment and showed no adverse effect on their physical condition.

This data suggests that electroshock therapy can be effective in treating the depression syndromes developing in patients with cerebrovascular disease. However, there is indication that a greater risk is involved than with physically normal individuals.

It is not known whether this greater risk is primarily a reflection of the diseased cerebrovascular system, the effect of this on the central nervous system, or the generalized cardiovascular disease implied by the occurrence of a cerebrovascular accident. Alexander, Gahagan and Lewis[1] reported that in necropsy studies of 4 patients who died during electroconvulsive treatment, significant coronary artery disease was found. They believe that, "the main cause of death in treatment is the failure of the circulatory system to withstand the suddenly increased demands, or the strain imposed at the time of treatment." However, they also state that less frequently, death can be attributed to failure of the respiratory and nervous systems.

Certainly, when there is the question of vascular disease being present, and such a presumption is reasonable in any patient over the age of 60, no hard and fast general rule can be adhered to. Each patient must be evaluated individually, and the necessity for electroshock treatment carefully weighed against the potential risk implied by a diseased vascular system. There are times when an agitated suicidal depression presents a greater threat to the life of a patient, than the stresses that electroshock treatment induces in a severely compromised vascular system.

Kalinowsky and Hoch[8] have stated that in the tonic phase of an electrically induced convulsion, the muscular contraction is usually symmetrical. This observation is valid in most instances, but does not appear so in our experience with patients who have had

hemiplegia, or other paretic phenomena, following cerebrovascular accidents. Five of our patients with hemiparetic residua had asymmetric seizures. The asymmetry was consistent and predictable. In the tonic phase of the electrically induced convulsion, the paretic limbs were elevated higher than the unaffected ones, and the patient's trunk usually curled to the unaffected side, that is to say, away from the hemiparetic side. Altering the polarity of the current flow did not alter the consistency of this pattern.

The significance of this phenomenon is not clear. It is possible that the asymmetric pattern is a direct effect of unilateral brain damage.

Paralysis Agitans. Three patients who had Parkinson syndromes were treated with electroshock for agitated depression.

CASE 13. A 65-year-old man with a severe Parkinson syndrome developed an agitated depression. After 7 treatments, the depression and agitation resolved. The treatments did not seem to alter the structural disease, except that with the lifting of the depression, the patient became more active physically.

CASE 14. A 62-year-old woman with an involutional depression developed a Parkinson syndrome. She was given a course of 9 electroshock treatments. Because of relapse after 4 months, 4 additional treatments were administered. The psychiatric symptoms were considerably ameliorated, but the course of the Parkinsonism remained unchanged.

CASE 15. A 63-year-old woman developed a severe Parkinson-like syndrome following prolonged treatment with Rauwolfia and Chlorpromazine for an involutional depression. Fourteen electroshock treatments were given, producing a marked improvement in her affective disorder. Concomitantly, the Parkinson-like syndrome disappeared. It was felt that the disappearance of the extrapyramidal signs was unrelated to the electroshock, but was the result of stopping medication with Rauwolfia and Chlorpromazine. However, subsequently, she redeveloped a mild degree of rigidity, cogwheel phenomena and alternating tremor of the upper extremities.

Discussion. Several authors have reported treating patients who had symptoms of paralysis agitans and an affective disorder. Tucker, Fleming and Raeder[16] treated 4 patients with "central nervous system degenerative diseases" including Parkinsonism. Wolff[17] mentions 2 patients with Parkinsonism in his series of chronically ill patients, Gallinek[5] described the treatment of a 64-year-old woman with symptoms of Parkinsonism and an agitated depression. Ehrenberg and Gullingsrud[3] mention one patient in their report. Savitsky and Karliner[11] treated 7 patients. These last authors noted a decrease in tremor in some patients following electroshock treatments, but no change in the cogwheel phenomena. In none of these reported cases were any adverse effects noted, and all patients showed considerable improvement in their affective disorder.

Results in the 3 patients of the present series were also favorable. The psychiatric disturbance was alleviated, and there were no adverse effects noted upon the neurologic disease. A transient improvement in the tremor and other signs of Parkinsonism in one patient occurred concomitantly with her emotional improvement.

Central Nervous System Syphilis. Three patients with central nervous system syphilis received electroshock therapy. One patient, Case 7, has been discussed in the cerebrovascular accident group. This form of therapy was successful in alleviating his psychiatric symptoms without affecting his neurological disability.

CASE 16. A 67-year-old man was admitted to the hospital for treatment of severe rage reactions and overtly aggressive behavior. Two years previously he had been treated with penicillin for active central nervous system syphilis. Cerebrospinal fluid studies in the present admission showed an elevated protein concentration, but no cells. He was given a total of 17 electroshock convulsions. This therapy was effective in diminishing his belligerent behavior and his rage reactions.

CASE 17. A 62-year-old man developed a depression syndrome following business reverses. For about a year his family had noticed

a marked alteration in his personality. He had gradually changed from an aggressive dominating person to a passive, retiring individual. His family had also noticed that he had become intellectually dull. Cerebrospinal fluid studies disclosed classic evidence of active general paresis. He was given 2 courses of penicillin treatment without change in the psychiatric picture. When he was admitted to the hospital, approximately 4 months after the second course of penicillin, he was severely depressed, tearful, insomniac, anorexic, had marked difficulties in memory and in intellectual function, and was precariously oriented. In addition, he was disturbed by compulsive, stereotyped, repetitive "teeth grinding" movements of his jaws. Neurologic study disclosed the above-mentioned organic mental syndrome, Argyll Robertson pupils and nystagmus. The cerebrospinal fluid had a pleocytosis, elevated protein, positive Wassermann and a first zone gold curve. He was given a third course of penicillin. When this was concluded, electroshock therapy was begun. After 6 electroconvulsive treatments his depression had lifted, sleep and appetite returned to normal, and the stereotyped, repetitive "teeth grinding" jaw movements had disappeared. Other than some increase in alertness, there was no significant change in the organic mental syndrome.

Discussion. Heilbrunn and Feldman[7] had unfavorable results in their attempt to treat 5 patients who had central nervous system syphilis. Not only was no improvement in the psychiatric picture observed, but 4 of the 5 individuals developed prolonged cyanosis and apnea after the seizures. Despite this adverse report, the psychiatric symptoms associated with general paresis have been treated by electroshock more extensively than those associated with any other structural disease of the nervous system. The consensus of numerous reports has been that this mode of treatment is quite effective, and relatively free of risk when syphilis of the central nervous system is present. Thus Petersen[10] treated 70 patients suffering from general paresis and effected improvement in 63 of them. Savitsky and Karliner[11], and Solomon, Rose and Arnot[13] have reported similarly. The 3 cases we have described showed marked improvement as a result of the electroshock therapy. No patient developed any complication from the treatment.

Spinal Cord Disease. Three patients who had severe spinal cord disease were given electroshock treatment because of affective disturbances.

CASE 18. A 58-year-old man was given 3 electroshock treatments for a depression syndrome. He then attempted suicide by leaping from a second-story window and sustained a cervical vertebral fracture, and an incomplete transection of the high cervical cord. Six weeks after this injury the electroshock treatment was resumed. After 17 additional treatments his psychiatric illness was markedly improved. The treatments had no adverse effect on the severe spinal cord lesion.

CASE 19. A 32-year-old man had an incomplete, thoracic spinal cord transection from an automobile accident. Three years later he developed a severe depression and attempted suicide. After 4 electroshock treatments, he was sufficiently improved to permit discharge from the hospital and continuation of treatment by psychotherapy. The treatment had no adverse effect on the spinal cord lesion.

CASE 20. A 48-year-old woman had a meningioma removed from the spinal cord at about the level of D_7. There was little recovery of function. She continued paraparetic and had pronounced impairment of all sensory modalities below the level of the lesion. Severe flexion contractures necessitated prolonged use of a hip spica cast. A second laminectomy demonstrated marked spinal arachnoiditis. During the 2 or 3 months following surgery, she became increasingly agitated and complained of excruciating pains in the lower extremities. In an attempt to alleviate the agitation, electroshock therapy was begun. After the third treatment, she was confused but surprisingly was able to move her lower extremities, and required less analgesic medication. This seeming improvement in her neurologic disability was temporary. After the ninth treatment, she demonstrated a full-blown paranoid psychosis. Electroshock therapy was discontinued. In the following 2 weeks the psychosis disappeared and she returned to her pre-treatment status. A second course of electroshock therapy was essayed one month later. After the fifth treatment the paranoid psychosis reappeared. An organic mental syndrome was evident after the twelfth

treatment. A suicidal attempt after the thirteenth treatment necessitated her transfer to a psychiatric hospital. The 2 courses of electroshock had no significant effect on the spinal cord disease.

Discussion. Two patients with severe spinal cord injuries were successfully treated by electroshock for agitated depression. One patient who had had a spinal cord meningioma removed, and had then developed an arachnoiditis, developed a paranoid psychosis when she was treated by electroshock for agitation. In none of these patients was the neurologic condition aggravated by the treatment.

Dystonic and Dyskinetic States. Four patients who had severe, almost incapacitating, dyskinetic movements resulting from structural disease of the central nervous system, were treated with electroshock. In 2 of these patients the treatment was instituted primarily because of concomitant agitation and depression. The other 2 patients were given electroshock therapy in an attempt to alter the neurologic disability.

CASE 21. A 48-year-old man had had severe dyskinetic, dystonic and dystaxic symptoms since the age of 12. Numerous procedures to alleviate these symptoms had failed. These included resection of the sternocleidomastoid muscle, pyramidal tractotomy, rhizotomy of the spinal accessory and upper 4 cervical nerves, and the like. He developed a severe depression syndrome. Fourteen electroshock treatments produced a marked remission in the psychiatric illness. Seven months later, however, the depression symptoms returned and he was given an additional 11 treatments. Again, the psychiatric illness resolved. The electroshock treatment had no objective effect on his physical disabilities other than some questionable improvement in co-ordination.

CASE 22. A 56-year-old man had intermittent, spasmodic torticollis for 12 years. He developed a severe depression 5 months before treatment. Concomitantly, there was a marked exacerbation of the torticollis. He was given 20 electroshock treatments. At the end of this treatment his mood was cheerful and optimistic, and although there was still considerable involuntary, spasmodic movement of the neck, he was able to hold his head erect most of the time.

CASE 23. A 58-year-old woman had a 4-year history of involuntary lip smacking and purposeless, restless movements of the body and extremities. These symptoms were exacerbated when she was emotionally tense. Twelve electroshock treatments were given. There was no significant effect on the involuntary movements.

CASE 24. An 11-year-old boy had a one-year progressive history of torsion of the body and disco-ordinated movements of the extremities. Seven electroshock treatments were administered without producing any change in his condition.

Discussion. Strauss and MacPhail[15] used electroshock to treat 20 women who had various tics. They reported improvement in 9 of these patients. On the other hand, Kalinowsky and Hoch[8] note that the results of treating patients for dyskinesias with electroshock are rather contradictory.

The secondary affective disturbance, present in 2 of our patients, was successfully treated with electroshock. However, the electroshock therapy neither exacerbated nor ameliorated the neurologic disability in the 4 patients. Minor improvement was noted in the performance of the 2 patients with concomitant psychiatric illness. This minor improvement seemed to reflect only an increased ability to voluntarily control the dyskinesias. This probably was a result of the amelioration of mood, and did not represent any true effect on the basic underlying neurologic condition.

Summary. 1. Twenty-four patients with structural disease of the central nervous system were treated with electroconvulsive therapy because of severe affective disturbances.

2. Fifteen of these individuals benefited significantly from this treatment.

3. Of 6 patients with intracranial neoplasms, treated with electroconvulsive therapy prior to establishing this diagnosis, one patient had a partial

remission of his depression for about 5 months. A second patient may have already had a meningioma, when he was first successfully treated with electroshock, one year prior to the establishment of the diagnosis of the intracranial tumor.

4. Exacerbation of neurologic disability, precipitated by electroshock treatment, made it necessary to terminate treatment in 5 patients with intracranial neoplasm.

5. Of 6 patients with cerebrovascular accidents, treated for depression from 3 weeks to 2 years after the ictus, 4 showed great improvement. Two patients died following electroconvulsive therapy. There was strong suspicion that the electroconvulsive therapy was causally related to the mortalities. It was not established whether the mechanism of death was through cardiac or central nervous system implication.

6. Three patients with Parkinsonism and depression responded favorably to electroconvulsive therapy, in that the depression was eliminated. The severity of the Parkinsonism was temporarily ameliorated in one case during treatment. This improvement was not considered an effect of the electroshock treatment.

7. Two patients with traumatic spinal cord disease and affective disturbances benefited from electroconvulsive therapy, without any effect of their neurologic disorder. One patient who had severe spinal arachnoiditis twice developed a paranoid psychosis during electroshock therapy. The electroshock treatment did not, however, exacerbate her neurologic disability.

8. Three patients with central nervous system syphilis benefited psychiatrically from electroconvulsive therapy, without any alteration of their neurological signs.

9. Four patients with dystonic and dyskinetic states were treated; 2 of these individuals were severely depressed. Electroconvulsive therapy in these patients relieved the depression, but did not alter the neurologic dysfunction. The other 2 patients did not have any psychiatric disturbance and derived no benefit from electroconvulsive therapy.

Conclusions. 1. Disease of the central nervous system *per se*, with the exception of known intracranial tumor, is not an obligatory contraindication to electroconvulsive therapy.

2. Electroconvulsive therapy can be highly effective in resolving severe psychiatric disturbances, despite the presence of disease of the nervous system.

3. Other than when an intracranial neoplasm is present, the use of electroconvulsive therapy does not appear to alter the neurological picture in patients with disease of the nervous system.

4. Electroconvulsive therapy, however, is definitely contraindicated in the presence of intracranial tumors. These patients develop a rapid, persistent and severe organic mental syndrome, and their neurologic disability is exacerbated.

5. The rapid appearance of a severe and persistent organic mental syndrome, during the course of electroconvulsive therapy, particularly in the young and middle age groups, should raise the strong suspicion of structural disease of the brain. In particular, the possibility of silent intracranial neoplasm should be carefully considered.

6. Electroconvulsive therapy may have a higher risk potential in patients with cerebrovascular accidents than in patients without evidence of vascular disease of the brain. Whether this higher risk potential is specifically related to cerebrovascular or to cardiovascular disease, is not known.

7. Hemiparesis resulting from cere-

brovascular accidents may lead to asymmetric seizure patterns. In the induced seizure, the paretic limbs paradoxically elevate higher than the unaffected ones, and the body turns to the normal side.

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SUMMARIO IN INTERLINGUA

Therapia Electroconvulsive in Patientes con Morbo Structural del Systema Nervose Central

1. Vinti-quatro patientes con morbo structural del systema nervose central esseva subjicite a therapias electroconvulsive a causa de sever disturbationes affective.

2. Dece-cinque de iste individuos beneficiava significativemente de iste tractamento.

3. In un gruppo de 6 patientes con neoplasmas intracranial, tractate con therapia electroconvulsive ante le establimento del diagnose de neoplasma, un experientiava un remission partial de su depression durante un periodo de circa 5 menses. In un altere caso, il es possibile que le patiente jam habeva un meningioma quando ille esseva primo tractate con bon successo per therapia electroconvulsive un anno ante le establimento del diagnose de meningioma.

4. Exacerbation del invaliditate neurologic, precipitate per le therapia electroconvulsive, fortiava le termination del tractamento in 5 patientes con neoplasma intracranial.

5. In un gruppo de 6 patientes con accidentes cerebrovascular, tractate pro depression inter 3 septimanas e 2 annos post le ictus, 4 monstrava bon grados de melioration. Duo patientes moriva post therapia electroconvulsive. Il habeva un forte suspicion que le therapia electroconvulsive esseva causalmente connectite con le mortalitate. Non esseva determinate si le mechanismo mortal implicava le corde o le systema nervose central.

(Continued on page 219)

ERYTHROCYTE AUTO-SENSITIZATION*

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Gardner and Diamond[3] have recently introduced the term "auto-erythrocyte sensitization" to describe their findings in a group of 4 women. These patients had in common a history of an abnormal response to bruising characterized by local pain, swelling and extension of the bleeding to adjacent areas of skin and subcutaneous tissues. In each instance, the syndrome had been initiated by trauma and hematoma formation. Distant, apparently spontaneous, ecchymoses of the skin were observed in 2 of these patients. Cerebral hemorrhages, gastrointestinal and genitourinary bleeding also occurred in 2 of the patients. The extensive ecchymoses and the concomitant systemic reactions differentiated the disorder from the relatively mild purpura simplex so commonly seen in women. Over a period of years, the condition displayed a tendency toward gradual amelioration. All studies relating to the coagulation mechanism of the blood gave normal results. On the basis of intradermal tests with whole blood, washed red blood cells, red cell stroma, plasma, serum, and protein fractions of the plasma, both from the patient and from normal controls, Gardner and Diamond concluded that they had demonstrated a tissue sensitivity to extravasated red blood cells and that the agent responsible was some factor in the red cell stroma. They postulated that in these cases a fixed tissue antibody reacts with red cell stroma to produce edema, increased capillary permeability and further extravasation of blood into the tissues. The lesion then spreads by the further contact of the red cells at the periphery with sensitized tissue. They do, however, suggest the possibility that a more diffuse vascular disease associated with the red cell sensitivity may be present to account for the clinical picture seen in these women. Attempts to desensitize these individuals with whole blood, washed red cells or red cell stroma were unsuccessful. In 2 patients, splenectomy was of no benefit. More recently, they observed 5 additional cases, all in women[2].

The concept that some allergic

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purpuras may be due to red cell auto-sensitization is of great interest. As a rule, allergic purpuras occur in association with certain signs of allergy such as erythema, urticaria or effusions of serum into subcutaneous or submucous tissues, joints or viscera. These characteristics are seen, for example, in Henoch-Schönlein purpura, erythema bullosum, urticaria pigmentosa and other conditions. Generally, the search for the offending agent, presumably an antigen, by means of the established techniques is fruitless.

Therefore, the provocative data presented by Gardner and Diamond warrant careful consideration. We have recently observed a young woman who suffered for several years from frequently recurring and disabling skin and subcutaneous ecchymoses. Evidence of erythrocyte auto-sensitization was sought by the techniques of Gardner and Diamond and the results obtained were of sufficient interest to warrant this report.

Case Report. B.D., an unmarried white woman, 27 years of age, was referred to one of us (I.W.) at the Albert Einstein Medical Center, Northern Division, in September, 1955, because of recurrent, extensive, spontaneous ecchymoses of the skin involving the extremities and occasionally the trunk. These were associated with systemic symptoms of low-grade fever, malaise and weakness. Her illness began in January, 1952, after she entered the United States Naval Reserve as a Wave. The personal and family histories were negative except that her father and 2 paternal first cousins had respiratory allergies. Soon after entering the service she received the usual initial immunization injections, including triple typhoid vaccine, without untoward reaction. On January 18, 1952, she was given a second injection of triple typhoid vaccine. The site of this injection in the left upper arm became markedly swollen and painful within the next 24 hours. Chills, malaise and low-grade fever were present. During the next few days an extensive subcutaneous hematoma of the left upper arm developed and was treated with antibiotics, incision and drainage. Healing was slow and protracted. On February 21, 1952, a third injection of triple typhoid vaccine was given in the right upper arm. At this site also, a painful spreading ecchymosis appeared. Simultaneously, the left upper arm, which had been gradually improving, became the site of a new ecchymotic lesion which ultimately spread to involve the entire extremity. For the next 4 months, until June, 1952, large hematomatous swellings developed in both upper extremities, requiring repeated incisions and drainage. Biopsy of the lesions on 3 occasions was reported as showing only extravasation of blood into the subcutaneous tissues.

After June, 1952, spontaneous ecchymoses began to appear on the lower extremities and subsequently on the trunk. Virtually without exception, these lesions occurred without trauma. They were preceded for a period of about 24 hours by a local sensation of tingling, burning and tenderness. This was followed by erythema and then a spreading area of ecchymosis which attained varying sizes over a period of 4 or 5 days. At any one time several ecchymoses of different sizes and stages of development were usually present. The typical appearance of these lesions is seen in Fig. 1. The patient suffered more or less continuously from malaise, fever between 99° and 100° F., and occasional bouts of nausea, anorexia, and vomiting. On two occasions there were bloody stools. There was no evidence of bleeding from other organs. Her menstrual cycles continued to be normal. In May, 1953, Roentgen examination of the left arm revealed a periosteal proliferation about 4 cm. in length along the lateral aspect of the left humerus at the junction of the middle and distal thirds. She was continuously confined in various military hospitals until September, 1953, when she was given a medical discharge from the military service. Extensive hematologic and other studies had been carried out, all with essentially negative results.

A number of military and civilian consultants examined her and various diagnoses were entertained. Anaphylactoid purpura, fibrinolytic purpura, necrotizing polyarteritis, Sanarelli-Shwartzman phenomenon, Henoch-Schönlein purpura, erythema nodosum, and allergic purpura due to typhoid vaccine sensitization were all considered. Because of the bizarre and undiagnosed nature of the disease, some observers considered the possibility of the factitial production of the lesions. However, competent psychiatric opinion, the appearance of new lesions under a plaster cast, and the opinions of 3 hematologists negated this diagnosis. In April, 1953, Dr. Thomas

Fitz-Hugh of the University of Pennsylvania suggested the possibility that her lesions might be due to auto-erythrocyte sensitization or fibrinolytic purpura. The patient's course continued to be marked by continuous disability because of recurrent ecchymoses, malaise, fever, and easy fatigability. Occasional transient joint pains were also experienced. She was unable to seek regular employment. Periods of remission lasting up to several weeks occurred on several occasions. One course of therapy with corticotropin appeared to cause some improvement but subsequent courses of cortisone were of no appreciable benefit. While she was still in the service, several blood transfusions were given with apparent beneficial effect.

When she was seen by us in September, 1953, the most striking physical abnormalities were numerous fading and fresh ecchymoses of all four extremities, the buttocks and trunk (Fig. 1). There was low-grade fever between 99° and 100° F. Skin and mucous membrane color was good. Healed incision scars were present on the extremities. The thyroid was not palpable. No superficial lymphadenopathy was found. The heart and lungs were negative on examination. The liver and spleen were not palpable. A neurologic survey was negative. Chest and gastrointestinal Roentgen-ray examinations were within normal limits. A roentgenogram of the left upper extremity no longer showed the calcific densities previously described. Blood proteins, albumin: globulin ratio, electrophoretic patterns of the serum, blood glucose, urea nitrogen, uric acid, calcium, phosphorus, alkaline phosphatase and thymol turbidity determinations were normal. Urinalyses were negative. Hematologic studies showed a normal blood count and sedimentation rate. The coagulation profile included the platelet count, clot retraction, prothrombin time, labile and stable factors, coagulation times of whole blood in

Fig. 1.—Typical appearance of spontaneous ecchymoses on lower extremities.

glass and silicone, as well as clotting time of blood diluted with saline in silicone tubes, prothrombin consumption, and thromboplastin generation tests. Tests for circulating anticoagulants and fibrinolysins were also done. All these studies were within normal limits and confirmed the results obtained previously in other laboratories. The Rumpel-Leede's test gave a 1-plus positive reaction on several occasions.

An interesting observation was made when the skin bleeding time was performed on the right forearm. The usual Duke technique was followed without venous stasis. The actual bleeding ceased in 3 minutes, 45 seconds. However, within 12 hours after the test, the patient noted pain, tenderness, and an erythematous swelling at the site of the puncture wound. About 24 hours later a painful ecchymosis approximately 4 cm. in diameter appeared. During the next 4 to 5 days this irregularly oval ecchymotic swelling about 95 by 55 mm. This continued to spread and its appearance after 5 days is shown in Fig. 2. By the eighth day the hemorrhagic lesion had extended over the entire forearm and reached beyond the elbow and wrist. Simultaneously, spontaneous ecchymoses appeared on the legs and trunk. By contrast, the 2 control subjects showed only local staining of the injected site, which did not spread beyond 25 mm., and faded rapidly by the fourth day.

PLASMA AND SERUM. Plasma was obtained from heparinized blood and serum from blood clotted at 37° C. for 2 hours. One normal control subject was used. Testing was carried out within several hours. The patient was tested with 0.01 ml. and 0.1 ml. of her own plasma and serum and those of the control. These all gave negative reactions.

HEMOGLOBIN. Hemoglobin solutions from the patient and from 2 normal controls were

Fig. 2.—Appearance of arm 5 days after intradermal testing with 0.1 ml. of unmodified whole blood.

hemorrhagic lesion extended to involve the entire forearm, which became extremely painful and swollen. This unusual reaction suggested a severe sensitivity to extravasated blood and appeared to simulate her clinical course. It was subsequently noted that such trauma as a mild ankle sprain was soon followed by a large ecchymotic area which, instead of subsiding within several days, spread widely so that the ecchymosis rather than the ankle sprain became the disabling factor. Because of these observations we proceeded to carry out the tests described by Gardner and Diamond for evidence of auto-erythrocyte sensitization.

Intradermal tests were done at various times with the following:

WHOLE UNMODIFIED VENOUS BLOOD. Venous blood was drawn from the patient into a siliconized syringe and 0.1 ml. immediately injected into her forearm. Two normal controls were treated similarly. Within 24 hours the patient's test site showed a deep purple, prepared according to Gardner and Diamond[3]. Tests with 0.05 ml. of these 3 solutions were negative in the patient as well as in the controls.

WASHED RED CELL SUSPENSIONS. Because of the severity of the reaction with 0.1 ml. of whole blood, the initial tests with washed red cells were performed with 0.01 ml. of 10% and 20% suspensions. No reactions occurred in the patient or in 2 control subjects. Subsequently, the test was repeated using 0.05 ml. of a 20% suspension of washed red blood cells. With this amount, an ecchymotic reaction appeared within 24 hours (Fig. 3), reached a maximum of about 60 by 100 mm. in 5 days, and faded gradually over a period of 2 weeks. Similar tests in 2 control subjects were negative. At a later date, 0.05 ml. of a 50% suspension of washed red cells of the patient and of 2 normal controls was injected. Marked ecchymotic reactions occurred in the patient within 24 hours, from all these tests (Fig. 4). The control subjects showed no reactions.

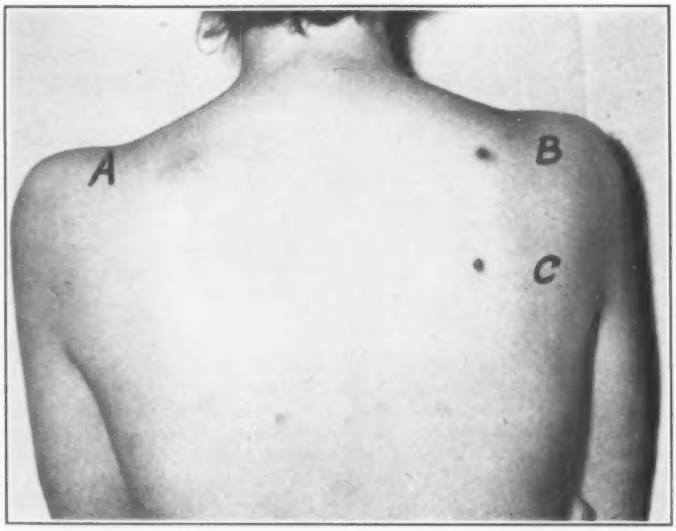

Fig. 3.—Appearance of the back 2 days after intradermal testing with 0.05 ml. of 20% suspensions of red cells of (*A*) the patient, (*B*) and (*C*) controls. Note the petechial and faintly ecchymotic reaction at *A*.

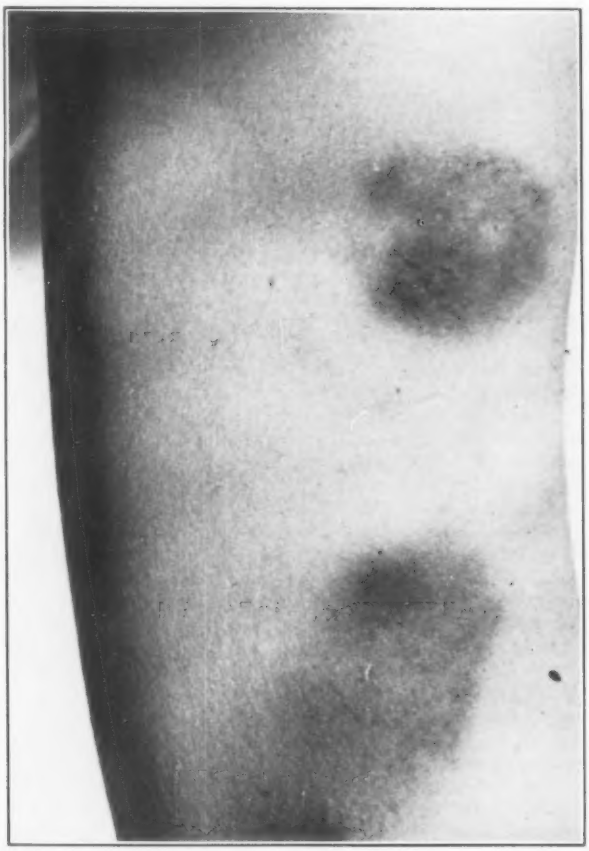

Fig. 4.—Appearance of patient's arm 24 hours after intradermal tests with 0.05 ml. of 50% suspensions of washed red blood cells obtained from the patient (*lower*) and a control (*upper*). Note the ecchymotic reactions to both tests.

RED CELL STROMA SUSPENSIONS. These were prepared from both the patient's blood and from a normal control, in a concentration equivalent to a 50% hematocrit of red cells, according to the method described by Howe[4]. The patient and 2 normal controls were tested with 0.02 and 0.05 ml. quantities of each of the preparations. All the tests were negative except for the site in which 0.05 ml. of the patient's stroma was injected. This showed a slight petechial reaction in the patient. Subsequently, the test was repeated using 0.1 ml. of the suspensions from the patient and 2 control subjects. In 24 hours, all 3 injection sites in the patient showed irregular areas of petechiae and ecchymoses, which reached their maximum size, about 40 by 50 mm., at the end of 3 days (Fig. 5). The control subjects gave negative reactions.

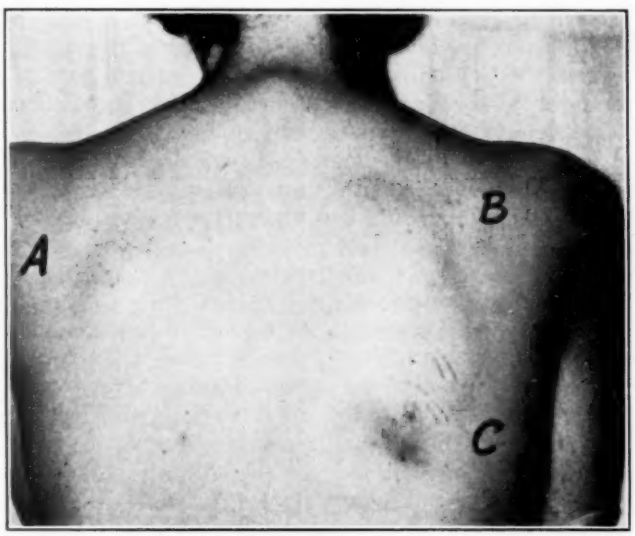

Fig. 5.—Appearance of the back 3 days after intradermal tests with 0.1 ml. of stroma suspensions equivalent to a 50% hematocrit. *A* and *B* represent stroma from control subjects, *C* from the patient.

Control tests with 0.1 ml. quantities of saline and Coca's solution as well as hyaluronidase were consistently negative. The whealing response to 2 dilutions of histamine diphosphate was not remarkable.

Passive transfer by the Prausnitz-Küstner technique was attempted in 2 recipients with negative results.

Discussion. The clinical picture and the results of the tests in this patient are very similar to the cases described by Gardner and Diamond[3]. Sensitization to the stroma both of her own red cells and that of other individuals of the same blood type was demonstrated. Trauma with extensive hematoma formation was the apparent initiating factor in the 4 women in Gardner and Diamond's series. In our patient the disorder began following hematoma formation resulting from injections of triple typhoid vaccine. It seems likely that subcutaneous hemorrhage incident to the injections and the subsequent surgical intervention served as the antigenic stimulus rather than the typhoid vaccine, although it is possible that the latter was in some way associated with this reaction. The lesions were characterized by initial erythema followed by a spreading ecchymosis that continued for as long as 2 weeks or more. This type of reaction does indeed suggest that due to the sensitiza-

tion of the tissues, extravasated blood causes edema and increased capillary permeability in adjacent areas. What ultimately halts the reaction is not clear although it is suggested by Gardner and Diamond that dilution with serum in the edema fluid reduces the concentration of red cells below a critical level.

Assuming that erythrocyte auto-sensitization is an allergic disorder, it is difficult to understand why so high a critical concentration of red cells or stroma is necessary to elicit the reaction. Because of the severity of the initial test with 0.1 ml. of whole unmodified blood, the next tests were done with smaller doses of less concentrated suspensions. It was only when at least 0.05 ml. of 50% concentrations of washed red cells in saline and equivalent concentrations of stroma were finally used that a clear-cut response was elicited. It is well known that 0.1 ml. quantities of any fluid injected intradermally may be excessive for test purposes and that extravasation of blood might occasionally be induced by this alone. However, ecchymoses occurred in our patient only when red cells or stroma were injected, but not after similar quantities of plasma, serum, hemoglobin solution, saline, histamine solution and hyaluronidase. Also none of the individuals who served as controls developed ecchymotic reactions, even when red blood cells or red cell stroma were injected. When attempts were made to desensitize the patient with injections of minute quantities of dilute stroma, subcutaneous injections were given. With each injection, painful spreading ecchymoses developed and the procedure had to be abandoned. A similar reaction was obtained when normal saline was injected subcutaneously. We believe that in contrast to injections into the relatively avascular derma, subcutaneous injections ruptured capillaries, and the resulting extravasated blood initiated a characteristic pattern of edema, capillary permeability and further extravasation, as was seen when red cells were experimentally introduced intradermally.

The occurrence of distant and spontaneous hemorrhages into the skin, chronologically following traumatic ecchymoses (or those induced in the course of blood-taking, testing procedures and the like) is difficult to explain. One may postulate the release from the site of the existing ecchymosis of a substance having the property of markedly increasing capillary permeability. In this connection, an analogy can be drawn to the widespread visceral petechial hemorrhages typical of fatal anaphylaxis and the Sanarelli-Shwartzman phenomenon.

The clinical picture seen in our patient has many of the features of Henoch-Schönlein purpura. The same is true of the 4 women described by Gardner and Diamond. This suggests that Henoch-Schönlein purpura may sometimes result from a mechanism of erythrocyte auto-sensitization.

This disorder differs from so-called "purpura simplex" in that patients with erythrocyte auto-sensitization are apparently rarely free of ecchymoses and that the lesions spread extensively as compared to the relatively limited and intermittent character of the lesions in the simplex variety. Moreover, in erythrocyte auto-sensitization a rare individual allergic predisposition or some associated complicating factor at the time of the antigenic stimulus, as for example, trauma or in our patient, typhoid injections, appears to be necessary.

While erythrocyte auto-sensitization of this type appears to be rare, it would be worthwhile to subject other cases of purpura to similar testing.

The phenomenon of "auto-sensitization" or "endogenous allergy" has in-

trigued allergists and others for more than 4 decades. The concept implies that specific substances within the body acquire allergenicity as a result of their denaturization or degradation through any one of a number of mechanisms. Trauma is the factor most frequently held responsible for such tissue change, but infections, abnormal endocrine products, malignant tumors, pregnancy, menstruation and cold have been implicated. The tissues most frequently undergoing such antigenic alteration include the blood, skin, eye, liver and kidney. The entire subject of endogenous allergy was reviewed up to 1946 by Urbach and Gottlieb[6]. Whitfield[7] was apparently the first to attribute erythemato-urticarial eruptions in 2 female patients to an auto-sensitization mechanism, resulting from the extravasation of blood in hematomas produced by trauma. Comparable cases were described by Barber[1] and Urbach[5].

No effective treatment for erythrocyte auto-sensitization has as yet been described. The results of steroid therapy are not impressve. Splenectomy does not appear to be indicated and was not found clinically efficacious in Gardner and Diamond's cases. Attempts at hyposensitization have so far been unsuccessful.

Summary and Conclusions. 1. A case of purpura is reported in which intradermal skin tests with suspensions of washed red blood cells or erythrocyte stroma produced delayed local reactions characterized by petechiae and extensive spreading ecchymoses accompanied by swelling and pain. These reactions occurred only when certain minimal concentrations and quantities were exceeded. Normal control subjects failed to react in a similar fashion.

2. The reactions were the same whether the source of the red cells and stroma used in the tests was the patient's own blood or that of some other individual. Accordingly, it is assumed that the patient represents a case of erythrocyte auto-sensitization.

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SUMMARIO IN INTERLINGUA

Auto-Sensibilisation de Erythrocytos

1. Es reportate un caso de purpura in que tests intradermal con suspensiones de lavate erythrocytos o stroma de erythrocytos produceva retardate reactiones local, characterisate per petechias e extense diffusive ecchymoses accompaniate per tumescentia e dolor. Iste reactiones occurreva solmente quando certe minimos de concentration e de quantitate esseva excedite. Normal subjectos de controlo non reageva similemente.

2. Le reactiones esseva le mesme quando le erythrocytos e le stroma usate in le tests proveniva ab le sanguine del patiente e quando illos proveniva ab le sanguine de alicun altere individuo. Ergo, nos conclude que le patiente representa un caso de auto-sensibilisation erythrocytic.

PROGRESS
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THE MANAGEMENT OF CLEFT-LIP AND CLEFT-PALATE PATIENTS

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"THE Cleft Lip-Cleft Palate syndrome is probably the most common serious congenital anomaly amenable to surgical correction"[54]. On birth certificates in the State of Pennsylvania for 1954, the three most frequently reported congenital anomalies were club feet, clefts of the lip or palate and finger-polydactylism (376, 303 and 131 respectively in 244,405 live births)[43]. Herniae probably occur more frequently than any of these[47]. So it would seem that practically every practicing physician is likely to come in contact with these patients or their parents. This paper is intended to present a broad picture of management for patients with clefts of the lip and palate, not particularly for those with specialized interest in this field, but rather for doctors who are not so closely associated with these problems.

First, conditions arising in the neonatal period will be discussed along with questions that parents are likely to ask. Next, the treatment of cleft lips will be considered briefly, and then the various aspects of cleft palate management will be considered in more detail. A plan of treatment will be outlined for the over-all care of these patients, and the care of the "complicated case" will be discussed. This will be followed by a summary of the current results.

In this way physicians who might be responsible for part of the care of these patients will have a comprehensive idea

of the problems which arise from their patient's cleft lip or palate. Also, doctors who are called upon to console anxious patients, friends or relatives might be able to give a clearer picture of the over-all problem and are less likely to contradict their colleagues.

It is hoped that the term "harelip" will be discarded, and the more scientific word "cleft" will be used in referring to these deformities of the lip and palate. This is desirable not only from a scientific point of view but also because of the stigma which has become attached to the use of the colloquial term[26].

clefts, in which the defect does not extend through the alveolar ridge (or tooth ridge), and *complete* clefts, where it does. Complete clefts are further divided into those which are unilateral and those which are bilateral. Victor Veau[87] has labeled these clefts as Type I, II, III and IV, as described in the legend below Fig. 2. The most commonly occurring cleft is a left unilateral complete cleft of the lip associated with a left unilateral complete cleft of the palate[25,31,32,59].

Any of the various types of cleft lip can be present in combination with any of the various types of cleft palate,

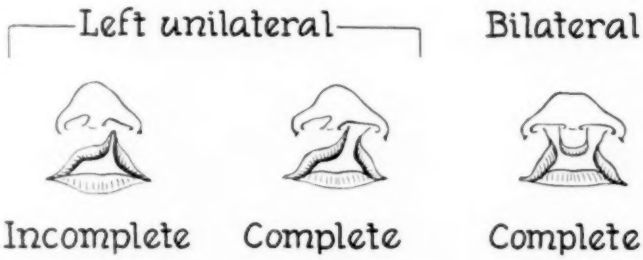

Fig. 1.—A simplified classification of cleft lips, dividing them into unilateral or bilateral, complete or incomplete clefts (depending on whether or not the defect extends *completely* through the entire lip and nostril floor). Note that even in the incomplete unilateral cleft the adjacent columella and ala nasi are distorted. Bilateral clefts may be complete, incomplete or a combination of the two.

In describing and recording clefts, a simple classification is valuable. Figure 1 illustrates a classification which divides clefts of the lips into those called *incomplete*, in which the lip is incompletely cleft and those called *complete*, in which the cleft extends all the way through the entire lip and the floor of the nostril. These clefts may be unilateral or bilateral. Bilateral clefts may be complete or incomplete or they may occur as a combination of the two.

Figure 2 illustrates a simplified classification for clefts of the palate. Again they can be divided into *incomplete* or clefts of the lip and palate can occur separately. Even with incomplete clefts of the lip, distortion is usually seen to involve the adjacent structures with widening of the nostril floor and distortion of the columella and ala nasi on the cleft side. In the same way, incomplete clefts of the palate may be associated with a submucosal cleft in the bone extending beyond the soft tissue defect.

THE NEONATAL PERIOD. If the patient with a cleft palate also has a short mandible, a real emergency can face the obstetrician and the pediatrician in the neonatal period. The findings of

micrognathia, microglossia and an incomplete cleft of the palate (sometimes known as the Pierre Robin syndrome)[69] can be associated with severe respiratory obstruction. The genioglossus muscle and other tongue muscles are unable to hold the tongue forward when the point of the chin is displaced posteriorly. Obstruction occurs at the base of the tongue, and occasionally this is severe enough to require a tracheotomy. This operation should not be taken lightly in a newborn infant. More frequently an adequate airway can be provided by positioning the baby's face downward so that his tongue will fall forward. A tongue stitch or a nasopharyngeal airway can provide temporary improvement. There are several more permanent surgical methods of management[6,29]. A real danger exists in this condition if an airway can be

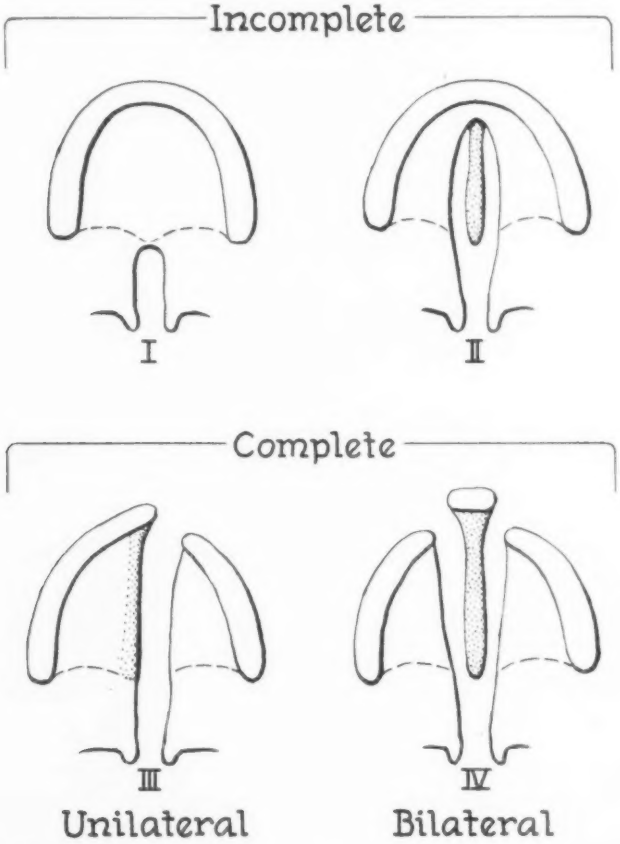

Fig. 2.—A simplified classification of cleft palates, again dividing them into complete or incomplete clefts depending on whether or not the alveolar ridge is cleft. Veau has called these Type I where just the soft palate in involved, Type II in clefts of the soft palate and the hard palate but not the alveolar ridge, Type III for the complete unilateral cleft and Type IV for the complete bilateral cleft. Note that the uvula is cleft in all types, that the cleft extends into both nostrils in Type II and Type IV and into only one side in Type III.

maintained only when the infant cries or struggles and if respiratory obstruction occurs whenever he relaxes. In this situation an infant can literally exhaust itself to death.

An unrepaired cleft of the lip or palate is a horrifying sight particularly to an emotionally labile mother. It is a terrible blow to parents who have built up hopes and joys for many months, and it gives rise to all sorts of doubts, fears and worries. Like as not, they have never seen such a condition before, and they wonder why it should happen to them, what they might have done wrong, what could have been done to prevent it, whether they should ever have any more children, whether this is the price of having married someone much older, and eventually what they should tell their child when he or she grows up and contemplates marriage. These questions are probably all answered best by the plastic surgeon. However, it is usually the obstetrician, the pediatrician or the family doctor who knows the parents more closely. They have already gained the confidence of the parents, and their advice and consolation are depended upon to a great extent. Conflicting information is damaging, so joint discussions with the plastic surgeon can be helpful to all.

In talking to parents, we usually point out that they have probably never seen an unoperated cleft lip or palate before. Few nonmedical people have, but they should be told that this is a fairly common condition and that a great deal can be done about it. They should feel that there are well-planned steps for its correction and that they can expect considerable improvement. Realistically, they should know that even with the best results perfection will not be reached.

The parents should understand that the complete cause is unknown. Falsehoods should be contradicted. They should be told that a cleft is not the result of wrong doing, maternal impressions, superstitions or anything that could have been avoided during pregnancy. Clefts in humans are not caused by any known communicable disease; the age of the parents does not seem to be a factor, and the only established causal influence is heredity[16,31,55]. Discussion of experimentally produced clefts is usually not mentioned. An interesting study of the possible connection between emotional stress and the occurrence of cleft palates has recently been published by Strean and Peer, 1956[78]. Cleft lip alone and cleft lip associated with cleft palate are usually inherited anomalies while the isolated cleft palate is inherited in relatively few cases (about 20%). W. B. Davis reported a positive hereditary history in 57% of 425 cases; Fogh-Anderson, 30 to 40% in 794 patients[25,31,75]. These percentages are probably incorrectly low because families have been reluctant to admit to relatives with congenital anomalies. We have one cleft palate child whose mother insists that her own cleft palate occurred after a fall down the stairs as an infant.

If there is no history of cleft lip or cleft palate in the family, we usually tell the parents that there is very little likelihood of their having subsequent children with the same deformity. With a negative family history, the chances of a patient with a cleft having children with the same deformity is obviously greater than if he did not have the cleft, but it is still very small. With a positive history of clefts occurring in the family, the incidence of clefts in subsequent children is much greater. In one Dutch town with considerable inbreeding, the incidence in the general population has been reported as high as one cleft per 100 births, so in this area the likelihood of

subsequent clefts in families where clefts already appear is extremely high[70].

One mother said that she understood the situation best when told that the cleft occurred as an accident in development. People know that accidents can happen to anyone so this seems to be a good word to use. In discussing future plans, parents are usually in no frame of mind to understand minute details, but they can feel that a well-organized plan of treatment is available to them.

Parents worry about feeding. It is a subject they usually know something about, and in this case it provides a good opportunity to bring them into the care of their child. They quickly achieve a feeling of accomplishment and confidence when they are taught a simple way to handle a seemingly difficult situation. This sense of *being needed* helps to establish a close and healthy relationship between the mother and her child.

A child whose only deformity is a cleft lip can usually suck and swallow with very little difficulty. When a cleft palate is present, the baby can swallow, but he is unable to build up a suction in his mouth and cannot prevent food from going up into his nose. Mothers should expect this and should allow extra time for feeding a cleft-palate child. It helps to hold the infant in a semi-sitting position, and because he swallows a good deal of air he needs frequent burping. A soft nipple with holes large enough to allow the milk to drip out slowly without having to be sucked out works well under most conditions. Some surgeons object to using nipples, feeling that the force of the tongue against the palate increases the width of the cleft. The Brecht feeder, a rubber tipped dropper, a spoon or a cup can also be used[54].

CLEFT LIP MANAGEMENT. Closure of the cleft lip is purely a plastic surgical procedure, and the time for operation is usually decided upon by the plastic surgeon in consultation with the pediatrician. Good surgery is essential for good results. Irreparable and conspicuous damage can be done by the surgeon who is inexperienced in this type of work. Furthermore, these are not emergency procedures requiring operation within 24 hours of birth; the child can feed well without surgical closure. With modern transportation and medical centers an experienced plastic surgeon should be within the practical and economic reach of patients in almost every part of this country.

Opinions vary as to when the cleft lip should be closed. Some plastic surgeons prefer to operate within the first 2 weeks of life if the child is in good condition. Red blood cell, hemoglobin and maternal antibody levels are higher at this time than at any other. If the operation is done early, the parents are able to take home a much more normal looking baby than would be possible otherwise[9,10,54]. Other plastic surgeons prefer to wait until the child is 1½ to 2 or 3 months old, feeling that the operation is safer when the child is older and is beginning to gain weight on its own. Also they feel that with structures a little larger a better result is possible, and that anesthesia is safer. It has also been pointed out that since the cleft lip operation falls short of perfection anyway, if parents live with a cleft lip patient for a few weeks they are more appreciative of any degree of improvement. This decision should probably be left up to the plastic surgeon who knows how the best results can be obtained in his hands with the greatest margin of safety[51,77]. Conditions should be ideal and anesthesia must be reliable. Local anesthesia is preferred by some[42,76,79]. The

pediatrician is relied upon to decide when the child is in good health and able to stand what might be a relatively long procedure. This decision should be based on the general condition of the baby, his weight, the presence or absence of respiratory infection, anemia, bleeding tendencies, and the possible presence of other congenital anomalies.

Reconstruction of a cleft lip is a complicated architectural procedure and aims at restoring normal contour of the entire area with as little damage as possible to parts that are destined to grow. Primary closure is sometimes planned in more than one stage. An attempt is usually made to make the nose symmetrical to produce a full even lip of good thickness with a slight flare or pout at the level of the vermilion. Further objectives include an even vermilion-skin border, a smooth vermilion, a deep upper buccal fornix, a good nostril floor and accurate muscular approximation with a minimal amount of scar. It is obvious that this is not an operation for the inexperienced surgeon, particularly since any degree of failure is glaringly conspicuous. As the lip grows, discrepancies of less than a millimeter became magnified, and structures such as cartilage, bone and musculature which are already distorted are likely to become more asymmetrical. Secondary corrective procedures may be desirable on an elective basis. Soft tissue deformities can be corrected at early school age, while extensive nasal deformities are sometimes best postponed until the patient has passed adolescence[21,54].

CLEFT PALATE MANAGEMENT. The decision concerning how and when to close a cleft palate is not a simple one. This is usually a decision for the plastic surgeon to make, and the majority of the cases will probably get the best results by plastic surgical closure. Many surgically closed cleft palate patients develop good speech and have a minimum number of dental problems. These patients are seldom seen by our dental colleagues. Others need general dentistry, orthodontia and replacement of missing or deformed teeth. On the other hand, the dental specialists see a great many patients in whom surgery was ill-advised, ill-timed or badly executed. These "surgical cripples" present a tragic picture. Many have had 8, 10 and 12 operative procedures and are left with severely deformed upper jaws, persistent perforations, and scarred, short immobile "soft" palates. We are very fortunate in having orthodontists, prosthodontists and speech therapists who can contribute immeasurably to their salvage.

In recent years, largely as a result of attention directed toward this tragic group of patients, cleft palate clinics have been developed for their care. The Lancaster Cleft Palate Clinic in Lancaster, Pennsylvania, for instance, is a nonprofit organization in which a team approach is used to very good advantage. The fields of plastic surgery, orthodontia, prosthodontia, pedodontia, speech therapy, psychology, pediatrics, otolaryngology, growth and radiology are at one time or another concerned with the care of these patients, some more so than others and each with its limitations. Working alone, a doctor can accomplish his purpose well, but in the process he might hinder the progress of another equally important or more important specialist or overlook the need completely. So it becomes essential in handling some patients for such a team to work together and to make calculated compromises[21]. Dr. Herbert Cooper, Director of the Lancaster Cleft Palate Clinic, has likened this situation to a symphony orchestra. As director his main

duty is to keep the sections in tune and playing in harmony. The melody must be carried by the proper persons at the proper time, and the bass must be kept from playing too loudly. Some instruments do well in solo; others need support, while none should dominate throughout. It is obvious that when discord arises, the final result is not very good.

In discussing this phase of the problem, the roles of the surgeon, the speech therapist, the orthodontist and the prosthodontist will be presented. Each has his aim and each his limiting factors.

Plastic Surgery. The palate does more than just separate the mouth from the nose. The valve-like function of the soft palate in conjunction with the superior pharyngeal constrictors is an integral factor in the mechanism used to vary sounds into what we call speech and in allowing us to swallow with ease[12,14,82]. Speech is a unique body function in that it is voluntary; it is almost completely a learned activity; it requires thought process but uses certain muscles by completely unconscious reflexes. The motions of the soft palate must be quick, complete, effortless and practically automatic if good speech is to be produced. The surgeon has the aim of building a solid barrier or partition anteriorly and a soft, pliable structure posteriorly which has adequate length and mobility. Too few people realize that in the majority of cases he should be completely successful in obtaining these aims. Good surgical results, furthermore, are far better than the good results achieved by an artificial appliance so far as speech and swallowing are concerned[26,41,51,71,74].

Scar tissue is one of the limiting factors which interferes with the achievement of this aim. Unfortunately, whenever tissue is cut, it heals with scar formation. The amount of scar will vary greatly depending upon the type of operation done, the gentleness with which the tissues are handled, the way in which they heal and the number of times the same tissues have to be subjected to surgery. "Bone crushing" techniques, carried out with haste and roughness, and with the use of heavy suture material, the loss of blood supply, necrosis of tissue, infection, and partial or complete failure of healing will leave tragic amounts of scar[4,29]. This scar will limit the bony growth of the maxilla and will interfere with the function of the soft palate[33,35]. Surgery carried out as atraumatically as possible should leave very little scar, and studies in these patients have shown little or no variation in bony growth[30,51,63,64]. It is difficult to be sure just how much damage is caused by operation because the cleft itself disturbs bony development. A cleft in a palate "is an insult to the growth and development of the cephalo-facio-dental pattern"[48]. Also there is considerable variation in: 1) the growth of the normal palate; 2) maxillary bone growth when a cleft is present; 3) the rate and the age when growth occurs in both the hard palate and the soft palate and 4) in the different types of clefts that occur. "As the face is cleft, so is the growth inclined"[48,81].

There are two reasons for bringing out these points. First, because of the possible surgical damage to growing bone, there is a strong feeling that operation should be postponed (particularly since about 90% of maxillary growth is completed by the age of six) or that surgery should be abandoned completely[20,37,48,50]. This has led to a desire to operate on these patients in the older age groups. On the other hand, if the patient learns to speak without having his cleft palate closed, he learns to use substitution sounds for the sounds he cannot make. The problem of teaching him how to stop

using these sounds, to learn how to use his newly repaired palate for the production of correct sounds, and then to use this speech reflexively becomes a very difficult one. The plastic surgeon is, therefore, urged to operate on these patients at an earlier age in this regard. "Once the patient has learned incorrect speech habits, the difficulties are increased a hundredfold" (Wardill)[76,89].

Various operations are recommended. Relaxing incisions are usually made laterally allowing the palatal tissues to be approximated in the midline without tension. Accurate closure of the muscular layer of the soft palate is essential for good results and if desired a lengthening operation can be done at the same time or at a later date. Many plastic surgeons prefer to close the cleft palate routinely at about 12, 14 or 18 months of age because they feel that the attainment of good speech is the most important aim and that with good surgery the damage to bone growth is small or insignificant. Others prefer to wait routinely until the patient is 4 to 6 years of age in order to allow for further bone growth and to follow closure of the palate with intensive speech therapy if necessarry. A third approach is to weigh each case individually, operating early on those patients showing rapid development of speech habits and good bone growth, and delaying operation in those patients showing retarded bone growth or speech development[5,8,30,51,54,59,63,64,66].

Beside the arbitrary limitations imposed by scar tissue, there are others which should be discussed. Some cleft-palate patients seem to have very little soft palate tissue. This is particularly true in wide, incomplete clefts and in those older cleft-palate patients whose palates have never been operated upon. Even though mechanical closure can usually be achieved in these patients, the closure is likely to be tight, and with atrophic musculature these palates do not function well. These patients are probably best treated by prosthodontia, and if this fails, surgery can always be invoked. Finally, some patients are very poor surgical risks for other reasons and are also best treated by prosthodontia[56,62].

Speech. One of the reasons for our present unsettled opinion concerning the best type of closure and the best time for closure is that it is very difficult to measure the degree of speech imperfection. Roentgenograms can be used to demonstrate millimeter differences in bone growth, but speech is an intangible product which changes with mood, environment and intelligence.

In general, poor speech in the cleft-palate patient is defective in three ways. It has a characteristic nasal resonance which is called "hypernasality." The patient literally talks through his nose, and vowel sounds become badly distorted. This is very conspicuous, and for the most part, it will persist so long as velo-pharyngeal closure (soft palate against pharynx) is incomplete. He is also likely to have two types of articulatory errors due to his inability to build up pressure within his mouth. Explosive consonants, called "plosives," (b, d, g, k, t, p) will be incompletely enunciated and the sound of other consonants, called "fricatives" (f, th, h, wh, v, s, sh, ch, z), is distorted. Combinations of these consonant sounds may also be defective. This is due to the leakage of air into the nose which is known as "nasal escape"[53,84].

When these three defects are present about the only sounds he can pronounce correctly are "m," "n" and the sound "ng" as found in the word "moaning." The word "mummy" sounds pretty good. In place of a consonant which he is unable to pronounce he may use a distorted laryngeal sound or he may

omit the consonant completely. So, the word "daddy" would sound like "aah-ee"[1,50,53,58,85].

There is a preponderance of opinion that the best speech results are obtained in those patients operated upon before speech patterns become well established, that is, prior to about 2 to 3 years of age. In fact, normal speech can often be obtained in these younger patients without the aid of specialized speech training. However, it should be obvious that "the mere insertion of an artificial palate . . . or, for that matter, the surgical closure of a palate . . . cannot be expected to enable the patient to speak correctly any more than the possession of a piano or violin would make the owner an accomplished musician" (Ottolengui[83])[11,18,41,51,63,88]. Speech correction after incorrect speech has become established is tedious, difficult and progresses slowly. A speech therapist for cleft-palate children usually requires specialized training and needs a great deal of insight and understanding. The patients are frequently very young, shy and withdrawn and at times are almost hostile with severe behavior problems. Correction is frequently needed at an age when the patient is just recognizing that he is different from other girls and boys and when he may have been teased unmercifully. Furthermore, his auditory perception may not be developed to the point where he can tell the difference between his own incorrect speech and the proper pronunciations. Unfortunately, there is a great difference between being able to pronounce sounds and words correctly, and using these words reflexively in conversational speech. The results of therapy are usually proportional to the interest and intelligence of the patient and his family. There is nothing quite so gratifying as to see the light in a child's face when he realizes that he can pronounce words he thought he would never be able to say.

If possible these children should not be put into classes with stutterers, or children with behavior problems or mental retardation. With proper instruction the child's parents can be very helpful in carrying out instructions at home.

Orthodontia. It is the aim of the orthodontist to preserve as many teeth as possible, to restore teeth that may be completely missing, to align displaced teeth into their normal positions and to adjust the maxillary arch so that good occlusion is achieved. This is desirable not only so the patient can chew, but also because the upper anterior teeth are needed for good speech and a normal appearance. When a cleft extends through the alveolar ridge there is a great likelihood for the teeth adjacent to the cleft to be distorted in shape and position. Children with cleft palates usually have poor teeth. These teeth are said to be "soft" and prone to dental caries (Cannon, 1951). Perhaps this is due in part to the added sepsis from nasal discharge and the patient's inability to keep this area clean. With traumatizing surgery and dental neglect this problem can be compounded. Cleft-palate patients need constant dental care if these teeth are to be preserved, and the teeth must be preserved if they are to be used for orthodontic correction, or if the patient is going to require prosthetic replacement of missing teeth or the use of a prosthetic speech appliance. Unfortunately "there are probably more dentists afraid of children than there are children afraid of dentists"[69]. Pedodontic care and dental surgery are frequently needed, though the attention provided by the family dentist will often be sufficient.

With complete clefts of the palate, as shown in Fig. 2, the entire upper den-

tal arch is likely to collapse much the way a brick arch would collapse if part of the arch were missing. This collapsed upper alveolar ridge should be expanded if ideal occlusion is to be achieved. Perfection in this regard may be hard to reach, due in part to the tendencies of the dental arches to revert to their former position. Furthermore there is often a disproportion between the size of the upper jaw and that of the lower jaw. A relative retrusion of the mandible is a frequent occurrence with incomplete clefts of the palate, whereas protrusion of the lower jaw is more frequently the case with complete clefts, particularly when they are bilateral clefts[3].

Major orthodontia is not usually started until the permanent teeth have erupted but there are certain conditions where orthodontic treatment should be started as soon as cooperation allows (Patton). This has been the teaching in most dental schools; however, there is increasing evidence to show that when the maxilla is cleft, much less force is needed to expand the upper alveolar arch. This condition has been compared to a permanent fracture of the maxilla. For this reason some orthodontists prefer to start major orthodontic treatment at 3 or 4 years of age or as soon thereafter as the patient becomes cooperative. Results are obtained more easily and quickly. Expansion at this early age requires prolonged use of a so-called retaining plate to maintain the new position[7,45,62,65,66,67,68].

Prosthodontia. It is the aim of the prosthodontist to replace missing or deformed teeth. In addition, he is able to cover perforations through the hard palate. These occur so frequently in the region of the alveolar ridge that some plastic surgeons will not attempt to close the cleft in this area and prefer to rely on covering the defect with a dental plate. Others feel that this opening is undesirable if it can be avoided because leakage of liquids and air into the nose will still take place, and cleanliness becomes a problem. The work of the prosthodontist becomes very difficult if the permanent teeth to which the denture is attached are in an advanced state of decay.

Many years ago surgery on cleft palates was extremely difficult and dangerous. Since this deformity is probably as old as man himself, it is not surprising that descriptions of various types of dental plates, obturators, prostheses, appliances and speech aids appear in much of the older literature. Today this is a highly perfected dental specialty. The work that has been done to salvage some of the "surgical cripples" has been wonderful. Malformed jaws have been filled out, good occlusion restored with proper dentures, and by using an extension on the posterior portion of the upper plate, the nasopharynx can be filled with a so-called "speech aid" or "speech appliance" and the soft palate replaced artificially. Velo-pharyngeal closure is obtained by teaching the patient to use the upper pharyngeal constrictors on the lateral and posteror pharyngeal wall for contact against this prosthetic appliance. Speech can be excellent; oral, nasal and dental hygiene improved, and appearance immeasurably helped. The effectiveness of such a prosthesis is limited when teeth are in poor repair and when there is scar in the upper buccal sulcus or when the soft palate is present as a band of fibrous tissue which gets in the way. If a "speech aid" is used, remnants of soft palate in the midline are likely to be a hindrance if their motion tends to rock or dislodge the prosthesis.

Enthusiasm for this technique of closure has led some prosthodontists to suggest prosthetic restoration in all

clefts of the palate and in some cases to begin using an upper denture in children at the age of 2 years[37]. It should be remembered that an artificial palate is never as esthetic as the patient's own tissues[19]. It should also be remembered that good speech following good surgery is probably better and more frequently achieved than good speech following insertion of the best speech appliance[86]. A good prosthesis is expensive, likely to be broken (by children) and needs replacement from time to time. These patients have poor teeth and when the upper teeth are lost in later life, it is very difficult or impossible to retain a complete upper denture in an edentulous upper jaw with a cleft, particularly if the speech aid is included. A patient who has built his entire speaking life around the use of a denture might find his environment totally and tragically changed when he is no longer able to retain an upper denture (Longacre, 1954). It is very difficult to make a prosthesis with a speech aid before the permanent dentition has erupted, so in these cases the patient may be unable to talk correctly for at least the first 5 or 6 years of life[42,61]. Finally it has been shown that years of contact between dentures and oral mucosa, particularly if motion is involved, has occasionally led to the development of cancer[49].

Other Specialties. The pediatrician is needed in evaluating the general health of these children. As high as 10% of cleft-lip and -palate patients will have other congenital anomalies which will need consideration[31]. Cleft-palate children as a whole tend to be malnourished, anemic and prone to respiratory infection. These conditions should be cleared up as much as possible prior to operation.

Because of the constant reflux of oral contents into the nose there is a high instance of chronic middle ear disease, and deafness occurs in many of these patients. (In 401 cases 45% had ear trouble, and 39% had a hearing loss as reported by Skolnik[73].) The service of an otolaryngologist and an audiologist are therefore of great help.

Severe psychological problems are likely to arise particularly in sensitive children or when parents reject the patient with a cleft or do not understand his problems. These patients are always open to ridicule, particularly from other children, and are likely to become withdrawn, shy and misunderstood or to develop severe behavior problems[23]. When these children cannot talk properly they sometimes refuse to talk at all. Mental retardation is frequently suggested under such conditions, even though it is not present. Psychometric examinations can be difficult and inaccurate under these conditions and should be interpreted with caution. One of our patients had been institutionalized for mental retardation until it was realized that he was completely toilet trained and was dressing himself as well as normal children his own age. Unfortunately no one had bothered to do anything about his cleft palate or to teach him to speak until this error was discovered.

Much of the analyses of bone growth and the possible detrimental effects of surgery on facial growth depends on cephalometric examinations and the comparison of cleft-palate children with "normal" children of the same age and socio-economic background. The services of a physical anthropologist or growth specialist have added tremendously to this aspect of the problem[48,75]. The study of postoperative or post-prosthetic speech has recently acquired the help of the radiologist using ordinary radiologic techniques and also through the use of cine-fluorographic-image-intensified roentgenology (or, in

other words, the study of sound moving pictures taken of a fluoroscopic screen by means of image intensification)[12,14,22,52]. Finally, the electronic engineer is now recording speech in such a way that pitch and intensity can be recorded graphically through audiographic techniques so that records and analyses can be made[80].

It should be obvious that this entire "team" is not needed for every cleft-lip or cleft-palate patient. It should be equally obvious that each member can be of tremendous service under certain circumstance[21,56]. The "team" approach is not only of great benefit to particular cases, but it also provides one of the best environments for teaching the various aspects of cleft-lip and cleft-palate care. Only by observing and working with specialists in other fields is it possible to understand their aims and limitations[90,91,92].

A PLAN OF TREATMENT. After operative closure of a cleft lip, the importance of bringing the patient up in a normal environment with the usual diet and activities is emphasized to the parents. Special protective attitudes and peculiar feeding routines will not prepare these children for the knocks and blows they will have to take as they grow up, and they are usually in for more than their fair share.

At about one year of age the situation is re-evaluated. If the child has a cleft palate, consideration is directed toward the type of closure which would best suit him, and the pediatrician checks his physical status with special emphasis on nutrition, anemia, respiratory infections, middle ear disease and the possibility of other congenital anomalies that might have been overlooked[17]. Base-line growth studies are made. At 18 months of age a definite decision can ordinarily be made as to whether a good surgical closure can be obtained. The facial bone growth and long bone growth is again checked. If the child is in good health, shows normal activity, and development, good facial bone growth and if he has palatal tissues which should allow complete closure with a long pliable palate, operation is recommended between 18 and 24 months of age.

Again, the operation should be done under ideal circumstances, with care and gentleness, and it requires about a week's hospitalization. Some surgeons prefer to keep these patients in the hospital longer, and some prefer to close the palate in more than one stage[8,39].

The child is usually discharged with elbow restraints and instructions concerning his diet and activity. By about 4 weeks after operation he is back to a normal life with no limitations on his diet or activity; again the parents are instructed on the importance of bringing him up as a normal child if possible and to avoid protective attitudes and unnecessary diets. At this stage the child is encouraged to start using his palate by teaching him mild sucking and blowing exercises such as blowing soap bubbles, sucking through a straw, blowing bubbles through a straw, playing a mouth organ and blowing a whistle, and the like. If the child has reached the stage of speech development, attention can also be directed in this line as well. An intelligent parent can be a great help and some experienced surgeons give very exacting directions about speech practice and exercises at home. With this type of home instruction MacCollum has found that in 130 of his best speech results 79% spoke with no nasality and 90% of these had received no speech training except that given by their parents. (Incidentally, Dr. MacCollum's mortality in 1,034 palatoplasties was zero.)[51].

If convenient, the speech therapist

interviews the patient 3 to 6 months after operation. Directions can be given for home instruction, arrangements made for active speech therapy if indicated and a recording of the child's speech can be made.

Under ideal circumstances a patient with a cleft lip and a cleft palate can have an acceptable appearance and can develop normal speech with two operative procedures and 2 weeks of hospitalization. Usually secondary procedures are needed to correct minor discrepancies in the lip repair at about early school age. Occasionally a secondary operation is needed on the palate to provide added length and to close minor perforations[20,46,54,57,76]. Orthodontia is usually needed in complete clefts of the palate (see Fig. 2) and prosthodontia is advisable when permanent teeth are missing or have to be extracted.

When facial bone growth lags appreciably behind skeletal bone growth, surgical closure of the cleft palate is postponed. The length of postponement depends on the degree of delay in bone growth, the status of speech development and the general condition and adjustment of the child. Under these conditions, if the child is developing a large vocabulary with serious speech errors, closure is advocated fairly soon. If speech development is slow, closure of the palate might be delayed until the age of 3 or 4 years[74].

With marked delay in palatal growth, or insufficiency of palatal tissue or the patient a very poor surgical risk, operative closure is not attempted and a prosthetic upper denture with a speech appliance attached is used from the very beginning. If good results are to be obtained with a prosthesis it is best to leave the soft palate and pharynx completely free of scar tissue. Should a prosthesis fail to improve speech or if it is not tolerated by the patient, an operation might then be done[37,61].

THE COMPLICATED CASE. The complicated case is frequently the product of neglect or poor surgery or both. These patients can be complete wrecks with scarred and distorted lips, misshapen noses, deformed upper jaws with extensive dental decay and malocclusion, mutilated palates, unintelligible speech, chronic ear infections with appreciable deafness, severe behavior problems, malnutrition and anemia. A certain percentage of cases will have other severe malformations to complicate the cleft-lip and cleft-palate problems. Other cases will be baffling in that they will have poor results, especially in regard to speech in spite of seemingly good and adequate treatment.

The large majority of patients will have normal intelligence and ability, and if given half a chance they make social adjustments remarkably well[72]. Without rehabilitation they are usually doomed so far as social and economic adjustment is concerned, and it is here that the "cleft-palate team" can be used to best advantage[21,56]. The rehabilitation, or rather, the "habilitation"[51] of these patients is most gratifying. One young girl reported recently that she was no longer eligible for state aid to cover her last operation because she was earning too much money and had Blue Cross and Blue Shield coverage. Similar stories are frequent.

Before a decision on a plan of treatment in these cases can be reached a thorough evaluation must be made. After the various findings in each case are discussed, the deficiencies that are present and the steps that should be taken to correct them are decided upon. A logical plan of treatment usually becomes obvious. Hearing tests and intelligence tests are ordered before a trial of speech therapy is begun.

General dentistry and oral hygiene are needed to clean up dental decay and gingivitis before orthodontia, prosthodontia or plastic surgery is started. Roentgenograms are used to check the position, excursion and competency of the soft palate, and through their interpretation a decision can be made between the advisability of further speech therapy or a secondary palate operation[13,15,36,40,63]. Routine cephalometric examinations have even brought to light certain conditions not usually found in the cleft-lip and cleft-palate patient and have so directed attention to unsuspected neurosurgical and endocrinological problems. Calculated compromises are necessary when overlapping fields of interest conflict. In the end one must not forget that the patient is a person. "It is more important to know what kind of a patient has the disease than to know what kind of a disease a patient has"[67]. The complexities of a board of experts should not distort the personal relationships between the patient and his doctor[21].

Results. Through the combined and coordinated efforts of those interested in cleft-lip and cleft-palate patients and an increasing amount of scrutiny in evaluating the various results, considerable progress has been made in this field. More plastic surgeons are getting better specialized training in cleft-lip and cleft-palate surgery. Specialized speech therapists, orthodontists and prosthodontists are becoming available and are better equipped to handle these cases. Patients have more numerous facilities at their disposal on both private and ward levels, in state-run, nonprofit, and private institutions. Clinical and laboratory investigation is probably at an all-time high. In 1952 a society was organized which is called the American Association for Cleft Palate Rehabilitation. Its present membership of over 400 includes men and women who are certified in many diverse fields of associated interests. They contribute a great deal and are trying to understand each other's problems and accomplishments.

As a result, good care is usually available for the cleft-lip and cleft-palate patient. Fewer "surgical cripples" are being seen, and the usual case has better function and appearance, social adjustment and economic independence[2,8,38,51,56,64].

Summary. An attempt has been made to discuss in broad terms the general problems of the cleft-lip and cleft-palate patient. Conditions arising in the neonatal period have been presented along with questions that parents are likely to ask. The management of cleft lips is considered briefly. The various aspects of cleft-palate management are outlined in more detail with a discussion of the aims and limitations of the plastic surgeon, the speech therapist, the orthodontist, the prosthodontist and other specialists concerned with the care of these patients. A plan of treatment has been suggested, and a brief discussion is presented on the care of the "complicated case." Without proper treatment the cleft-lip and cleft-palate patient is ordinarily handicapped for his entire life. With correct therapy most of these patients can achieve not only good health but also a good social, marital and economic status.

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(Continued from page 195)

6. Tres patientes con parkinsonismo e depression respondeva favorabilemente al therapia electroconvulsive. Le depression esseva eliminate. In un caso le severitate del parkinsonismo se meliorava transitorimente durante le tractamento. Iste melioration non esseva attribuite al therapia electroconvulsive.

7. Duo patientes con traumatic morbo del medulla spinal e disturbationes affective beneficiava ab le therapia electroconvulsive, ben que sin effecto super lor disordine neurologic. Un patiente con sever arachnoiditis spinal disveloppava psychose paranoide a 2 occasiones durante le therapia electroconvulsive. Sed le therapia electroconvulsive non exacerbava le invaliditate neurologic de iste patiente.

8. Tres patientes con syphilis del systema nervose central beneficiava psychiatricamente ab le therapia electroconvulsive, ben que illes experientiava nulle alteration de lor signos neurologic.

9. Quatro patientes con statos dystonic e dyscinetic esseva tractate per therapia electroconvulsive. Duo de iste individuos esseva severmente deprimite. Le therapia electroconvulsive alleviava le depression in iste patientes sed non alterava le dysfunction neurologic. Le altere 2 patients in iste gruppo habeva nulle disturbation psychiatric e obteneva nulle beneficio ab le therapia electroconvulsive.

Le datos permitte le conclusion que morbo del systema nervose central per se, con le exception de casos de cognoscite tumores intracranial, non es necessarimente un contraindication a therapia electroconvulsive.

OPHTHALMOLOGY

UNDER THE CHARGE OF
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CENTRAL ANGIOSPASTIC RETINOPATHY AND CENTRAL SEROUS CHORIORETINITIS

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THE occurrence of episodes of edema in the macular region with consequent relatively transient disturbances of vision of rather characteristic type has been recorded by a number of authors under various titles, such as "central recurrent retinitis," "retinitis centralis annularis," "preretinal edema," "idiopathic flat detachment of the macula," "central angiospastic retinitis," "retinitis centralis angioneurotica," "capillaritis" and "choroidosis centralis serosa." The authors agree on the nature of the visual disturbances, which include metamorphopsia, micropsia, blurring and reduction of vision of varying degree, the observation of a dark spot or cloud in the center of the visual field (positive scotoma) and acquired hyperopia. But they differ considerably in their views on the mechanism of production of the edema and, as can be judged by the terminology employed, in their interpretation of the location of the edema in or under the retina. The descriptions of central angiospastic retiropathy by Gifford[20] and of central serous chorioretinitis by Kitahara[41] are illustrative of the different viewpoints.

Gifford[20] considered that spastic constriction of the smaller retinal arterioles or capillaries resulted in edema in the retina itself, particularly in the nerve-fiber layer, and that transient hyperopia was caused by actual elevation of the retina. He noted that a pronounced circular reflex was seen to surround the macular area in several of his patients. He thought that this indicated an elevation of the internal limiting membrane of the retina by edema fluid. Gifford and Marquardt[21] based their belief in the angiospastic nature of the retinal lesion on the presence in their patients of a tendency to peripheral angiospasm, usually a hereditary constitutional anomaly.

Kitahara[41] stated that central serous chorioretinitis is characterized ophthalmoscopically by a circumscribed, sharply demarcated retinal edema which represents a collection of serous exudate between the retina and the choroid. Within this edema there is seen frequently a yellowish gray spot, which represents the primary focus of disturbance in the choriocapillaris. In the later stages of the process, numerous gray-white dots are strewed through the edematous area and are presumed to be precipitates on the posterior surface of the elevated retina. Kitahara[41] thought that the lesion was

caused by tuberculosis or some other infection.

Rauh[59], Streiff[67] and Seitz[66] thought that there were sufficient grounds for considering central angiospastic retinopathy and central serous chorioretinitis to be essentially different disease processes. However, most other authors seem to use the two terms more or less interchangeably, their choice of title seeming to depend largely on their concept of the etiology of the lesion. Recent articles on this subject deal particularly with the pathogenesis of the edema, with its location and with its relation to the development of chronic macular degenerations.

It is generally recognized that not infrequently subjective symptoms precede by a considerable period the development in the macula of a sufficient amount of edema to be recognized ophthalmoscopically. The use of the Amsler[1] grid or of a modification of it described by Münchow[50] may indicate the presence of an organic lesion to explain complaints which might otherwise be considered to be functional. Metamorphopsia and micropsia can be demonstrated readily on such a grid. Amsler[1] stated that micropsia is present always in central serous chorioretinitis. The edema from the choriocapillaris or the retinal pigment epithelium raises and distends the basal attachment of the cones and separates them so that fewer perceptive elements are stimulated by a given object than would be the case in a normal retina. Goldschmidt[24] stated that he had been able, by demonstrating the failure of the patient to recognize Haidinger's brushes (an entoptic phenomenon), to diagnose typical central serous chorioretinitis in cases in which the lesion had not been discovered by ordinary tests. Priestley and Foree[56,57] stated that, long before ophthalmoscopic changes are visible, angiospasm in the retinal vessels can be demonstrated by the study of Scheerer's phenomenon, the entoptic perception of one's own blood cells circulating in the perimacular capillaries and in the closest precapillary arterioles and postcapillary venules. Jaeger and Nover[39] called attention to the disturbances in light and color sense which are characteristic of central serous chorioretinitis. In my experience, the reduction in the immediate dark adaptation in the early stages is indicated by the ability to demonstrate in reduced illumination a central scotoma which is not present in bright light. Seitz[66] noted that the gray positive scotoma observed subjectively by the patient changes to a yellowish spot with a green center when the patient is looking at a bright background and to a deep blue, violet or purplish red spot with a brighter center when looking at a dark background.

LOCATION OF THE LESION IN THE RETINA. *Involvement of the Macula.* Although it is possible, no doubt, for a similar process to occur in other parts of the fundus, the lesions which are diagnosed as central angiospastic retinopathy or as central serous chorioretinitis always involve the macula. As pointed out by Wolkowicz[72] and by Duke-Elder[16], edema is prone to settle in this region because the thickness of Henle's layer and its ability to swell permit the collection of large quantities of fluid. Duke-Elder added that the avascularity of the central retina with absence of capillaries limits the absorption of the edema fluid.

In Walker's[70] opinion, the edema comes primarily from the choroid. He stated:

> The arteries of the choroid have few branches of intercommunication and, therefore, possess to a considerable degree the ability of localized response. The macular area perhaps more than any other region responds in such a localized fashion, indicat-

ing the presence of a highly specialized vascular bed, probably controlled by a single posterior ciliary artery. Any involvement, spasm, sclerosis, inflammation, toxic influence or any combination of these affecting the vascular supply of this specialized area might cause a serous or hemorrhagic extravasation in the choroid. This extravasation passing through the lamina vitrea into or beneath the retina would produce a localized, elevated, non-inflammatory lesion at the macula.

Wybar's[73] studies of the vascular anatomy of the choroid did not lend support to Walker's thesis. Wybar said that, although each arterial branch has its own area of supply, there is no rigid anatomic segmentation of the choroidal circulation. The short posterior ciliary arteries are not true end arteries. An examination of casts of the choroid injected with neoprene did not reveal any structural differences between the portion of the choriocapillaris underlying the macula and any other part of the choriocapillaris at an equal distance from the optic disk. The submacular part of the choroid does have, however, a greater aggregation of arterial branches from the posterior ciliary arteries. Wybar concluded that there does not seem to be any clear-cut anatomic evidence to support the view that the selective localization of choroidal disease is attributable either to the involvement of isolated ciliary arteries or to peculiarities in the vascular architecture of certain parts of the choroid.

The Level of Retinal Involvement. Because the disklike positive scotoma seen by the patient was equally sharp whether the pupil was small or dilated and because vision was within normal limits, Guist[28] concluded that the retina itself must be normal and that the lesion causing the scotoma must lie right in front of the retina. He assumed then that there was a collection of fluid between the retina and the vitreous. Gissy[22] observed a case in which the positive scotoma and the abnormal retinal reflexes disappeared suddenly following apparent rupture of the internal limiting membrane of the retina and escape of the fluid into the vitreous. Bedell[3] and Evans[18] also thought that the edema was preretinal in location.

Elwyn[17] thought that, because the color of the retina in the edematous area changed very little or took on a darker red or dark grayish tinge, the fluid was primarily in the deeper layers of the retina and seeped through to lie beneath the retina. Because of his patients' inability to perceive Haidinger's brushes, Goldschmidt[21] placed the edema in Henle's layer of the retina. Savin[63] agreed that the main swelling was located in Henle's layer. Walker[70] stated that slit-lamp examination of his patients revealed an edematous, elevated retina. He was not able to demonstrate an overlying detachment of the vitreous, a flat detachment of the macula or an elevation of the pigment epithelium. In the opinion of Priestley and Foree[56], the evidence furnished by the study of the entoptic phenomena, Scheerer's phenomenon and Haidinger's brushes indicates that the edema is limited to the area between the inner nuclear layer and the internal limiting membrane of the retina.

Walsh and Sloan[71], Kitahara[41], Duggan[15] and Riehm[60] localized the edema under the retina. The fact that in most cases vision can be improved by plus lenses suggests that the fluid collects under the pigment epithelium rather than between the pigment epithelium and the retina proper, as it does in serous detachments of the retina. Goldmann[23] thought that his slit-lamp examinations indicated that the main collection of edematous fluid lay between the retina and the choroid, but he noted also a slight detachment of the vitreous over the edematous retina.

A number of authors, such as Bain[2], Davenport[13], Streiff[67], Seitz[66], Wolkowicz[72], Klien[43] and Mitsui and Sakanashi[49], seem to think that in some cases the edema comes primarily from the choroid or the choriocapillaris and collects under the retina, while in other instances the edema is located primarily in the retina. It seems probable that, in the more severe cases at least, edema starting primarily in either of these locations will later involve both. In many cases, therefore, it will be difficult clinically to determine the site of the primary lesion.

In a group of 51 cases considered to be instances of so-called central angiospastic retinopathy in which slit-lamp studies were made, Mitsui and Sakanashi[49] included seven in which the lesion was presumed to be quiescent, since only "a slight roughness of the pigment epithelium in the macular region" was found, and four in which the lesion could not be classified definitely. In the remaining 40 cases, the authors found active lesions of three different types. The visible changes in 22 cases were interpreted as indicating a circumscribed serous detachment of the retina with clear fluid between the retinal pigment epithelium and the retina proper. In 11 cases, the fluid appeared more opaque and the lesion was interpreted as a circumscribed serofibrinous detachment of the retina. In 7 cases, there seemed to be a circumscribed edema of the retina itself. In the authors' opinion, subretinal exudation and exudative detachment of the retina are not likely to be present in a primary retinal lesion. Actual angiospasm of retinal arterioles gives rise to edema in the inner layers of the retina, and the cloudiness lasts only 3 or 4 weeks. Subretinal exudation is characteristic of the lesions described by the authors; the edema of the retina is in the outer layers and it may persist for several months. These facts suggest that the primary lesion is in the choroid and that central serous chorioretinitis is a more appropriate diagnosis than central angiospastic retinopathy.

Klien[43] stated that functional vascular disturbances in the macular region may give rise to lesions involving the retina only, the choroid only, at least primarily, or both the choroid and the retina simultaneously. Central angiospastic retinopathy, in which Klien assumed apparently that the edema is confined to the retina proper, remains a clinical diagnosis, since its histopathology is not known. The histologic picture of the early stage of Klien's "central angioneurotic chorioopathy" is that of a serous or hemorrhagic extravasation from the choriocapillaris which accumulates beneath the pigment epithelium, the retina proper, or both. Organic changes in the choroidal vessels are either absent or insignificant, and inflammatory signs are missing. In the advanced or residual stage there is a fibrous subretinal mound which may be partly covered by pigment epithelium, and there are defects in Bruch's membrane. Small foci of round-cell infiltration may be scattered through the choroid behind the main lesion. The essential features of the histologic picture of the subacute stage of central angiospastic chorioretinopathy are coexisting serous extravasations from the paramacular retinal vessels and from the choriocapillaris of the posterior polar region and irritative proliferation of the pigment epithelium. There are no signs of inflammation. The end result of these extravasations, which at times may be hemorrhagic, are mounds of proliferated pigment epithelial cells and fibroblasts from the choroid which have organized the extravasated material. There is no destruction of the choroid underlying the

lesion, but there may be some destruction of the retinal neuro-epithelium.

RELATION OF CENTRAL SEROUS CHORIORETINITIS TO DISCIFORM DEGENERATION OF THE MACULA. Among the conditions which must be differentiated from central serous chorioretinitis, Keeney[40] mentioned senile and juvenile idiopathic degeneration of the macula and juvenile disciform degeneration of the macula. Czukrász[12] noted that some instances of the tapetoretinal pigment degeneration seen in elderly patients may represent the residuals of an episode of central serous retinitis which was not noted by the patient or was not recognized by the ophthalmologist because the complaint of metamorphopsia was not accompanied by ophthalmoscopically visible changes in the macular region. Walker[70] stated that it is probable that between the two extremes of central serous chorioretinitis and senile disciform degeneration of the macula "varying degrees of functional or organic choroidal vascular involvement account for many different types of macular lesions." Duggan[15] added to his report of 6 cases with acute lesions simulating central angiospastic retinopathy, reports of 4 cases which he called "chronic choroidosis centralis serosa" and of 3 cases of disciform degeneration of the macula, which latter, he said, differs only in degree from the mild lesions of choroidosis seen in young adults.

In their discussions of central serous retinopathy, Bennett[4] said: "It is possible that the elevation, in certain cases, may not subside and may even enlarge further, becoming paler as the overlying tissues atrophy, producing a variety of the condition known as 'juvenile' disciform degeneration of the macula . . . this condition in turn graduating insensibly into the 'senile' form of disciform degeneration," and Doggart[14] stated: "The advent of macular hemorrhages mentioned in some case reports will serve as a reminder that central serous retinopathy has important points in common with senile massive exudate at the macula, if due allowance is made for the fact that the latter condition attacks retinae rendered more vulnerable by reason of senile vascular changes." And also: "In favorable cases the fluid absorbs within a few weeks, but the rate of resolution varies considerably among different subjects, so that years may elapse before any flattening is manifest."

Klien[43] noted that the histologic picture of the residual phase of "central angioneurotic choriopathy" is indistinguishable from that of senile disciform macular degeneration. And Verhoeff and Grossman[69] had said some years before that disciform degeneration is due to some disturbance, possibly only temporary, in the choriocapillaris of the macular region. A hemorrhagic extravasate can occur between the pigment epithelium and Bruch's membrane, undergo organization and produce an ophthalmoscopic picture typical of senile disciform degeneration of the macula. This is probably the usual pathogenesis of the disease. A serous exudate beneath the pigment epithelium may be the cause of the juvenile type of disciform degeneration; so-called central serous retinitis may have a similar origin, the degree of pressure of the extravasation determining the ophthalmoscopic appearance of the lesion.

PATHOGENESIS OF THE EDEMA. Most observers agree that the formation of edema in the macular region in cases of central angiospastic retinopathy and of central serous chorioretinitis is initiated by a vascular lesion of some type. Thus Seitz[66] said that such a circumscribed disease process must result from a disturbance of the terminal circulation or of the vasomotor nerves.

The exudate forms first between the choriocapillaris and the pigment epithelium; accompanying or resultant histolysis causes an increase in the permeability of the lamina vitrea and the pigment epithelium, so that the fluid has access to the retina. In his opinion, the small choroidal focus seen in all cases of central serous chorioretinitis in the depths of the edematous area is the starting point of the disease process. Greeves[27] thought likewise that the condition is due to a small paracentral focus of choroiditis with secondary edema of the retina. Duggan[15] thought that lesions of edematous type in the retina or in the choroid are due to increased capillary permeability, which in the end is the result of local capillary and tissue anoxia. The primary changes in the arterioles, such as excessive arteriolar constriction, are "physiologic in nature but pathologic in degree." The retinal changes sometimes found in association with primary choroidal lesions are probably due, Duggan thought, to the passage of a histamine-like substance from the subretinal edema into the retina.

Buxeda[8] agreed with Horniker[36] that the primary lesion in cases of central angiospastic retinopathy is spasm of the capillaries of the macular region. Gifford and Marquardt[21] thought that the spasm might involve either the capillaries or the smaller retinal arterioles with resultant ischemia and edema of the macula. Elwyn[17] agreed that the primary cause of the edema is vascular constriction. But, in his opinion, the small arteries in and near the macula, and not the capillaries, are spastically constricted. Such a constriction results in dilatation of the capillaries distal to the constriction and a state of "peristasis," as had been suggested by Horniker[36], with transudation of fluid into the surrounding tissue.

According to Horniker[37], Kitahara[42] agreed that the entoptic phenomena observed in cases of serous central chorioretinitis are caused by narrowing of the retinal capillaries in the macular region. However, Kitahara[42] thought that the narrowing is not primary but is secondary to a serous exudate between the choroid and the retina. Similarly, Bonaccorsi[5] thought that the disturbance of color vision which occurs before there are visible ophthalmoscopic signs is due to a toxic stimulus affecting the sensory layers of the retina. The associated irritation of the pigment epithelium explains the serous collection in the early stages of the disease. Later, increased permeability of the choriocapillaris leads to the formation of the cloudy exudate which is characteristic of the more advanced stages of the process.

In her discussion of "central angioneurotic choriopathy," Klien[43] said: "The complete lack of organic vascular changes and the absence, clinically as well as histologically, of inflammatory signs and of other pathologic processes which could produce such profuse serous and occasionally hemorrhagic extravasations from the choroidal vessels, suggest the functional nature of the disease." She added that it is not known why transudation from the choroid leads first in some cases to detachment of the pigment epithelium and in others to detachment of the retina. With regard to central serous retinopathy, Doggart[14] thought that there must be an increase in permeability of the macular capillaries, especially of the choroidal network which nourishes the juxtafoveal region. Theoretically, this increased capillary permeability could be caused by locally produced or circulating toxins or by capillary stasis induced by arteriolar spasm with resultant anoxic damage to the capillary walls. Hamed[29] noted that retinal edema in general is a manifesta-

tion of either capillary or tissue damage by anoxemia or toxemia.

Severe or recurrent episodes of central angiospastic retinopathy may eventuate in the formation of a macular hole. Croll and Croll[11] described the mechanism of production of a late posttraumatic macular hole; spasm of the retinal arterioles with secondary vasodilatation and increased capillary permeability results in edema first in the nerve-fiber layer and later in the ganglion-cell layer with the formation of cystic spaces. Carlberg and Gausland[9] observed a lesion quite like so-called idiopathic central serous retinitis which seemed to follow an electric shock through the temple. They remarked that it seemed as if the retina "primarily reacts by edema in the macular region, pretty well independent of which type of injury has been inflicted, and independent of whether it is a question of an injury of a more general and toxic nature, or one that seems to be more local."

ETIOLOGY OF CENTRAL ANGIOSPASTIC RETINOPATHY AND OF CENTRAL SEROUS CHORIORETINITIS. Horniker[37] concluded that retinitis centralis angioneurotica (central angiospastic retinopathy) does not have a uniform etiology but is rather the expression of a hereditary constitutional peculiarity of the vascular system which causes it to react in a certain way to stimuli. Similarly, Gifford and Marquardt[21] thought that lesions of this type were apt to develop in individuals who exhibited a high degree of peripheral arterial spasm. Duke-Elder[16] stated that a number of conditions almost certainly enter into the etiology of central serous retinopathy; the most common one is probably capillary damage by toxins. Although some cases are best explained on an angiospastic basis, in others the element of spasm seems to be lacking. "My own impression," said Duke-Elder, "is that most of the cases are toxic, probably of an allergic nature and it may be of some significance that the majority of those which I have seen have had a highly positive skin-reaction to tuberculo-protein, a reaction which, of course, need not necessarily be specific."

Central Angiospastic Retinopathy as a Psychosomatic Process. The unusually large number of cases of central angiospastic retinopathy which occurred among the members of the armed forces, especially among naval personnel, during World War II, stimulated an extensive study of the possible causes of the condition. In a report summarizing the experiences of a number of observers, Cordes[10] stated that various etiologic factors had been discussed but that no conclusive cause had been established. The possible causes that received the most attention were the effects of exposure to excessive amounts of sunlight, allergic reactions from tetanus and yellow fever immunization and emotional upset with vasomotor instability, combined with overuse of tobacco, and resultant angiospasm. As Cordes noted, in the service there is ample opportunity for emotional upset, worry, fear and excessive smoking; the combination in an individual with an unstable vasomotor system could produce angiospasm. But these factors seemed to be excluded in some cases. Excessive exposure to light seemed to be rather conclusively ruled out as a causative factor. In this connection Irvine[38] described solar retinitis as a sharply demarcated, small, nonrecurrent lesion of the macula in an eye which has been exposed to excessive radiation. The evidence is against the assumption that there are cumulative effects of exposure to light. Therefore, remissions and exacerbations of symptoms favor the diagnosis of angiospastic phenomena.

Harrington[30] reported his observations in 40 cases of central angiospastic retinopathy among naval personnel; 26 had a residual hole in the macula. He found that anxiety was a factor common to all cases. He thought that psychic trauma is an important and frequent cause of autonomic instability, which was present in all his cases. Psychic trauma in a susceptible individual can produce, in his opinion, as profound organic changes in connection with the autonomic nervous system as extremes of temperature, anoxemia and direct physical trauma. In a later paper, Harrington[31] stated that he had personally studied nearly 100 cases of central angiospastic retinopathy and that there was definite evidence of vasomotor instability in all cases in which the peripheral vascular system had been investigated. He said: "It should be obvious that vasospasm which is radiometrically measurable in the extremities in susceptible persons is capable of producing physiologic and even permanent pathologic changes in a tissue as sensitive to anoxia as is the retina."

In a still later paper, Harrington[32] classified central angiospastic retinopathy as an ocular vegetative neurosis, "the physiologic accompaniment of constant or periodically recurring emotional states. The chronicity of an emotional tension alone is what makes the condition morbid." He realized that any autonomic stimulus of sufficient severity and duration can produce the condition, but he thought that the most frequent stimulus is psychic trauma. Psychiatric studies have revealed almost uniform anxiety states, he said, often of considerable severity; "even in peace time, the psychosomatic aspects of the disturbance are quite evident to fairly casual study." I am inclined to agree with this statement.

Zeligs[74] made a psychosomatic study of the occurrence of central angiospastic retinopathy in military personnel and reported 4 cases in each of which "fear and anxiety induced by combat played a prominent role in the patient's life, especially at the time the ocular symptoms first developed." He said: "Neurophysiologically, fear or anxiety initiate disturbances of higher cerebral centers, which, via hypothalamic pathways, produce changes in the sympathetic nervous system, giving rise to transient or maintained arteriolar constriction. . . . The duration of this response depends upon the intensity and persistence of the provoking stimulus."

Borley, McAlester and Lower[7] reported seeing among naval personnel almost 50 cases of macular lesions which they thought were caused either by infection or by exposure to bright light. They said that psychic factors might have been operative in some of the cases. It is possible that the 10 cases reported by Lucic[46] under the title of "juvenile disciform degeneration of the macula" may have been more severe lesions of the same general type as those reported by Harrington[30]. They all occurred in men between the ages of 19 and 37 years on active service in the navy. Microscopic examination of one of the involved eyes revealed "a mass of organized tissue between the lamina vitrea and the pigment epithelium. . . . Serum exudate surrounded the mass of tissue. The lamina vitrea was ruptured, and the choroid was somewhat thickened and infiltrated with lymphocytes." The author stated that the clinical appearance of some of the lesions suggested that the exudation might have been the result of a local neurovascular disturbance in the retina. Histologically, however, it seemed rather definite that the primary seat of the reaction was in the choroid.

Rusodimos[62] reported 7 cases of central angiospastic retinopathy, 5 in women and 2 in men; all had neurotic manifestations; only one smoked. Hartmann[33] called attention to the fact that, in psychosomatic phenomena, at times the emotion is not a sudden one, but consists in an almost permanent emotional tension, stress and strain so-called. Vascular disturbances, such as spasm of retinal arteries, are caused at times by psychologic factors mediated through the vegetative nervous system. Prolonged spasm may lead to the development of central angiospastic retinopathy.

Nicholls[51] also classified central angiospastic retinopathy as a psychosomatic disease. He reported 6 cases but thought that the disturbance was confined to the retinal circulation in only 3 of them. There was a definite anxiety factor in all 6, anxiety being defined as the effect of emotional stress. In discussing the occurrence of macular edema following extraction of cataract, Nicholls[52,53] expressed the opinion that the predisposing cause is vascular instability in the retina, the choroid or both, in the macular region, partly at least brought on by the surgical procedure, and that the precipitating cause is in some cases anxiety, possibly producing angiospasm, and in others, at least in part, prolapse of the vitreous through the pupil. Anxiety was a factor in 6 of Nicholls'[53] 8 cases; 3 of the 6 had vitreous prolapse also.

The Role of Allergy. Bonnet, Paufique and Bonamour[6] thought that central serous choroiditis is a special manifestation or mode of development of macular choroiditis due to various causes; the appearances are suggestive of tuberculosis, but tuberculosis cannot be demonstrated in all cases. Japanese authors have always stressed the importance of tuberculosis in the etiology of central serous chorioretinitis. Kitahara[41] said that the usual cause is tuberculosis or an unknown infection. The tuberculin reaction was positive in 42 of the 51 cases studied by Mitsui and Sakanashi[49]; it was 3 plus in 12, 2 plus in 5, 1 plus in 20 and plus-minus in 5. These latter authors thought that the lesion represented an allergic reaction rather than a direct tuberculous or similar infection. Bennett[4] was inclined to think that an infection of some sort was the most likely cause. It is of interest that Freed[19] and Schrire[64] reported as complications of Rift Valley fever lesions which they interpreted as central angiospastic retinopathy. However, the lesions seemed to be rather atypical.

Doggart[14] said that the processes assumed to underlie the formation of the edema in central serous retinopathy can be fitted readily into the allergic framework. He quoted Scuderi[65] as postulating an allergic explosion for which the way has been paved by an attenuated tuberculous focus. Loewenstein[45] maintained that, though it is very difficult to prove an actual spasm of the small macular vessels, there is no doubt that a central angioneurotic retinopathy does occur. However, it is probable that intraretinal and subretinal edema comes primarily from the choroid. Its formation is initiated by allergic capillary spasm, most commonly tuberculous. An allergic inflammatory reaction, tuberculous or nontuberculous, Loewenstein stated, is always characterized by a primary narrowing of the smallest vessels with edematous imbibition of the surrounding tissues.

Nonbacterial allergies may also be responsible for episodes of central angiospastic retinopathy or of central serous retinopathy. Rosen[61] observed the development of central serous retinopathy in several cases following vaccination for smallpox. He regarded this as an allergic response with specific

localization in the macula. Plumer[55] reported a case of probable central angiospastic retinopathy with recurrent episodes possibly caused by allergy to peanuts. Similarly, I have seen recurrent episodes of transient edema of the lids, conjunctiva and macular retina as an allergic reaction to the ingestion of pork.

According to Parry[54], Ko[44] suggested that central serous retinitis might be due to a pathologic photosensitization of the central retina. Wolkowicz[72] thought that the chain of events in central serous retinopathy closely resembles a nonspecific focal allergic reaction, and he based his attempts to reproduce the picture in the eyes of experimental animals on the assumption that the macular lesion represents an urticarial wheal. The eyes of rabbits were sensitized to light by the intravenous injection of eosin and were exposed to carbon-arc light one week later. Wheals developed which were quite similar ophthalmoscopically to central serous retinopathy and which histologically proved to be exudate apparently involving the retina primarily and accumulating ultimately beneath the retina to produce a detachment. Fluid was not present between the retinal pigment epithelium and the choroid. This suggested that the choroid did not share in the allergic reaction.

Wolkowicz[72] noted that emotional shock factors were present in the 2 (rather atypical) clinical cases that he reported. On the basis of his clinical and experimental findings, he concluded that the area of edema involves foremost the nerve-fiber layer when the initial vascular insult is limited to the retinal arterioles and that the lesion is an allergic vessel reaction of which exudation is the most striking phenomenon. Etiologic factors are numerous, but all follow a common pathologic pathway. Hollenhorst[35] collected from the files of the Mayo Clinic 74 cases classified as central angiospastic retinopathy. Thirty patients were said to be very tense or nervous, 17 had allergic manifestations and 11 had both allergic tendencies and a tension state.

It cannot be assumed, however, that the problem of the etiology of central angiospastic retinopathy and of central serous chorioretinitis is entirely solved. Vail[68] stated: "Based on my experience, I am not entirely satisfied with the psychogenic basis of angiospasms and believe that further studies will show an organic basis for the puzzling disease." And Bennett[4] said: "Although some cases of central serous retinopathy show evidence of ex- or endogenous mental complexes, and others give a history of other allergic conditions or vasospastic diseases (such as peptic ulceration, chilblains, angina), this is by no means always the case. Again, stress, neurosis, and allergy are the lot of so many of mankind today that their presence in association with disease may often be merely coincidental and of no aetiological significance."

TREATMENT. The prognosis for more or less spontaneous recovery of normal or almost normal vision is good in the average case of central angiospastic retinopathy or central serous chorioretinitis. Most observers agree, however, that severe or recurrent episodes may eventuate in considerable permanent loss of central vision. The methods of treatment generally recommended were quite well outlined by Doggart[14]: vasodilators, barbiturates, extra vitamins, removal of foci and avoidance of cold, worry, excitement and tobacco. Vaccines and short-wave diathermy, which he mentioned, are not in such general use. However, Doggart said that he had "never seen a case of this disease unequivocally respond to treatment." Nicholls[52] stated that vasodilators are

indicated in the treatment of central angiospastic retinopathy and that it is important to have the aid of the psychiatrist and of social service. Harrington[31] remarked: "The evaluation of planned psychotherapy, in the few instances in which it was possible to apply it, is difficult, but it seemed to be unusually effective."

McLean, Gordon and Koteen[48] noted in 1951 that 3 cases of central serous retinopathy treated with subconjunctival injections of cortisone recovered promptly and completely. The same authors[26] 2 years later were still of the opinion that central serous retinopathy responds well to steroid-hormone therapy. However, Purnell and Leopold[58] reported that 2 cases they treated with systemic cortisone were not improved. Hobbs[34] stated that the edematous exudate in central serous retinopathy has been seen to disappear more rapidly under treatment with cortisone than would have been expected otherwise, in a few instances within a matter of hours. He noted that 16 of 20 cases reported in the American literature for 1951 were said to have been improved by cortisone therapy. He treated 5 cases with subconjunctival injections of cortisone. Complete recovery took place within 12 days to 4 weeks. Hobbs thought that the expected course had been materially shortened in three of these cases. In 1956, Gordon[25] reported that a case of central serous retinopathy of more than 3 weeks' duration improved rapidly on prednisone with return of vision to 20/15 and loss of the central scotoma, and McLean[47] stated that this condition responds well to corticosteroid therapy if treatment is started early.

In discussing the treatment of central angiospastic retinopathy, Hollenhorst[35] said that, if the episode has occurred in a tense individual following closely on some unusual emotional upset, a vasospastic origin is assumed and vasodilator therapy and mild sedation with small doses of phenobarbital are advised. The use of tobacco is interdicted. Regulation of life so as to reduce tension and anxiety is urged. Avoidance of exposure to cold is recommended. Intravenous injection of triple typhoid vaccine is the preferred method of inducing vasodilatation. Three to five fever treatments are sufficient usually to initiate resolution of the edema. Treatment can be continued with orally administered nicotinic acid or 3-pyridine methanol (roniacol) although, in Hollenhorst's opinion, these and other similar vasodilators "do little more than perform a psychotherapeutic role until the natural recovery period of the disease restores the vision to normal."

According to Hollenhorst, recent and fairly mild cases, especially those of apparently allergic origin, respond well to corticotropin. If the lesion does not start to improve in 5 days, further treatment with this hormone is useless. Cortisone or hydrocortisone may be used in similar cases, but their effect, in Hollenhorst's experience, is less rapid and less constant than that of corticotropin. Their use need not be continued for more than 2 weeks. Occasional cases, particularly those of allergic origin, in which the lesions are of several months' duration and are refractory to other therapy, seem to respond to histamine administered intravenously; but an acute lesion may grow worse under histamine therapy, Hollenhorst noted. Antihistaminic drugs, such as benadryl, pyribenzamine and chlortrimeton, have been used with some success in patients with allergies.

Summary. It is probable that central angiospastic retinopathy and central serous chorioretinitis present different and distinct appearances to ophthalmoscopic and especially to slit-lamp exam-

ination, although the differences are not clearly defined as yet. Some observers think that the etiology and pathogenesis of the two lesions are different also. However, it seems more likely that either may be under given circumstances a psychosomatic manifestation or an allergic reaction. Functional arteriolar constriction from whichever cause seems to be the most probable local basis for the development of the edema. It is not clear why this constriction affects the retinal vasculature in some instances and the choroidal in others.

In the average initial episode, the edema tends to diminish rapidly and vision returns to normal or near normal. At most, a small relative paracentral scotoma remains. However, after several recurrent episodes, or even perhaps after a single particularly severe episode, a state of chronic edema may persist and hemorrhages may be added, with the ultimate development of a lesion practically identical with circinate retinopathy or disciform degeneration. I have watched such lesions develop.

Recovery from a single episode is more or less spontaneous. But absorption of the edema seems to be hastened by treatment of the angiospastic cases with vasodilators and of the allergic cases with adrenal corticosteroids. The prevention of recurrences would seem to be particularly important for the preservation of central vision. Careful evaluation of the patient's reaction to stress and strain as well as of his physical status is necessary if this is to be accomplished.

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PHYSIOLOGY

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SEMINAR ON THE HYPOTHALAMUS

Introduction. J. R. BROBECK, PH.D., M.D. (Department of Physiology, University of Pennsylvania School of Medicine). Mr. President, Ladies and Gentlemen: The hypothalamus is the portion of the brain situated ventral to the thalamus, superior to the pituitary gland, and medial to the internal capsule; it is bounded rostrally by the lamina terminalis in the midline only, and caudally by the caudal border of the mammillary bodies. From the thalamus it is rather well demarcated but its rostral and caudal limits are poorly defined. Rostrally it is continuous with the preoptic region and structures of the orbital surface of the hemispheres. Caudally it gradually merges with the tegmentum of the brainstem.

Examined in cross section the hypothalamus is seen to have two main parts, the central gray substance continuous with the gray matter surrounding the ventricular system also in other parts of the brain, and the lateral hypothalamic area containing myelinated fibers as well as unmyelinated fibers and cells, and continuous with the reticular formation of lower levels. Connections of the hypothalamus are interesting in that the more obvious tracts serve as yet unknown functions, while poorly defined or still undiscovered pathways seem to conduct most of the activity to and from this region.

Prominent nuclei, in addition to the mammillary bodies of unknown function, are the supraoptic nuclei which belong to the posterior pituitary system complex, the ventromedial nuclei believed to be related to feeding behavior, and the paraventricular nuclei of uncertain function.

Generalizations about this part of the brain have, in one instance, assigned it to the autonomic nervous system, or, in another case, have made it a center for integration of somatic and visceral responses to emotion. Both of these characterizations have merit, but they both fail to include other important aspects of hypothalamic physiology. The most useful generalization at present appears to be that the hypothalamus is a regulator of certain unconscious processes of the brain, especially those involving exchanges between the body and its environment. These include heat exchange, water and electrolyte balance, and energy metabolism in general. The hypothalamus is also able to direct the course of the intermediary metabolism; this it does through its regulation of the secretory activity of the endocrine glands.

In the papers of this informal symposium our attention will be given to the question of how the hypothalamus regulates (1) the exchange of heat, and of water and salt, and (2) the thyrotrophic and adrenocorticotrophic secretions of the anterior pituitary gland.

Heat Loss and Heat Production in the Dog with Posterior Hypothalamic Lesions. H. T. HAMMEL, PH.D., and J. D. HARDY, PH.D. (Department of Physiology, University of Pennsylvania

School of Medicine). Simultaneous calorimetric measurements of heat production and heat loss of normal dogs and dogs with hypothalamic lesions have been carried out in cold, warm and neutral environments. The experimental procedure permitted minute by minute observation of skin temperature, rectal temperature, water loss from skin, water loss from lungs, oxygen consumption and heat loss from skin. After short periods of adjustment the normal dog was able to adjust heat loss and heat production to identical values at all environmental temperatures (+10° C. —40° C.). The shivering threshold for the normal dog was observed to be at an average body temperature (0.8 rectal temperature + 0.2 skin temperature) of 37.2° C. The panting threshold was at an average body temperature of 37.8° C. The impaired dog showed residual ability to raise metabolism upon exposure to cold with a threshold of about 35° C. The animal was apparently not shivering during cold exposure. Following anesthetization, the impaired animal showed a decrease in metabolism with lowered body temperature with a Q10 of 2.2. It is believed under these conditions the animal was truly poikilothermic. Deep anesthetization of the normal animals revealed decreased metabolism with lowered body temperature with a Q10 of 2.25. Upon exposure to warm environment the impaired dog had a threshold for panting at roughly 39.5° C.; the rate of increase of water loss by panting was not sufficient to maintain constant body temperature.

The Effect of Oxytocin and Vasopressin on the Excretion of Na, K and Cl by the Kidney. FRANK P. BROOKS, M.D., and MARY PICKFORD, M.D. (Departments of Physiology, University of Pennsylvania School of Medicine, and University of Edinburgh). It has been recorded that whatever the stimulus applied, both active factors of the posterior pituitary are released simultaneously. The proportional amounts of the two vary, but always more oxytocin than vasopressin is liberated. The action of these factors on the composition of the urine has been re-examined, bearing in mind the possibility that oxytocin has usually been used in inadequate amounts, and that perhaps the effect of the two factors acting simultaneously should be considered, rather than the effect of either acting alone. Observations were made on conscious dogs, and oxytocin given as a single intravenous injection in doses of 4 to 15 mμ./kg. body weight, or infused intravenously at 0.01 to 0.02 mμ./kg./min. Vasopressin was given as single intravenous injections of 0.2 to 0.4 mμ./kg. body weight. During water diuresis oxytocin had little effect on the excretion of Na, K or Cl, but at resting rates of urine flow caused a marked increase in Na and Cl excretion. Vasopressin, unless given in large doses, had little effect on Na or Cl excretion at either high or low rates of urine flow. There is some indication that if oxytocin and vasopressin are given together Na excretion is increased at all rates of urine flow. Oxytocin always markedly increased diodone clearance, but did not affect creatinine clearance. If oxytocin and vasopressin were given together the clearances of both diodone and creatinine remained unchanged.

The effect of oxytocin was paralleled by that of a hypertonic solution of sucrose given intravenously in volume sufficient to cause antidiuresis. During water diuresis sucrose caused an increase in Na excretion only if the inhibition of urine flow was prolonged. At resting rates of flow Na excretion increased almost immediately. In a dog with diabetes insipidus, whatever the rate of urine flow, sucrose administra-

tion did not increase Na excretion, though the dog responded like a normal one to a moderately large dose of oxytocin.

The Hypothalamus and Thyrotrophic Hormone Secretion by the Adenohypophysis.* S. A. D'ANGELO, PH.D., and R. E. TRAUM, B.A. (Department of Anatomy, Jefferson Medical College, Philadelphia). The hypothalamo-hypophyseal-thyroid interrelationship was critically evaluated in adult female rats by determination of thyroid hormone secretion rate (biologic decay of thyroidal I^{131}) and TSH concentrations in blood and adenohypophyses (stasis tadpole bioassay) after placement of bilateral electrolytic lesions in the anterior hypothalamus. Lesioned rats (3 to 4 weeks after operation) were fed propylthiouracil (PTU) in the basic ration for 3 weeks to sacrifice, with unoperated controls pair-fed to insure equivalent goitrogen intake. In lesioned animals, thyroid hyperplasia was found to be partially inhibited and titers of circulating TSH decreased. The lesions, however, failed to prevent the massive discharge of TSH from the pituitary which characteristically follows inhibition of thyroid hormone formation in the rat. In a parallel experiment, lesioned rats (lesions deep in the anterior hypothalamus and impinging on the median eminence) were fed unrestricted amounts of a normal diet. Seven weeks after operation, these animals and controls were given a single injection of I^{131} (25 microcuries) preparatory to measurement of the *in vivo* thyroidal radioiodine release. Counts made once daily, over 4 days, revealed that the rate of thyroidal I^{131} release was slowed in lesioned animals (biological half-life, 3.5 days as against 1.7 days for controls). Histologic regression of the thyroid and decreased blood TSH levels were also found. Weights of adenohypophyses were also decreased but TSH concentrations remained within the normally high limits shown by controls.

The results indicate that both production and release of TSH from the pituitary are curtailed by extensive lesions in the anterior hypothalamus and that thyroid hormone secretion is secondarily reduced. The absence of marked differences in TSH concentrations of the pituitary between lesioned and control rats further suggests that this trophic mechanism has a high measure of residual function despite anterior hypothalamic deficit.

Further Observations on the Hypothalamic Regulation of ACTH Secretion. S. M. MCCANN, M.D. (Department of Physiology, University of Pennsylvania School of Medicine). Our previous investigations demonstrated that rats with severe diabetes insipidus, as judged by increased water intake, fail to show a significant ascorbic acid depletion in response to the following stresses: unilateral adrenalectomy, epinephrine, histamine, or Pitocin. These results were interpreted as indicating a blockade in the release of ACTH in rats with diabetes insipidus. Pitressin was capable of eliciting ascorbic acid depletion in such preparations. The effect of Pitressin in these animals has been confirmed in the present study. Pitocin at a similar dose is ineffective. The adrenal cortices of these rats with permanent diabetes insipidus appear to be less sensitive than normal to intravenously administered ACTH. For this reason, rats with diabetes insipidus were tested 48 hours after the operative interruption of the supraoptico-hypophysial tract. Such rats also fail to respond to nonspecific stimuli, such as unilateral adrenalec-

*Supported, in part, by grant A–432, National Institutes of Health, PHS.

tomy, histamine, epinephrine, or Substance P with ACTH release as determined by ascorbic acid depletion. They are more responsive to the effects of Pitressin than rats with permanent diabetes insipidus, responding to intravenous injection of as little as 0.25 to 0.5 pressor units/300 gm. rat. The sensitivity of these animals to Pitressin is similar to that of animals in which ACTH release is blocked either by morphine-Nembutal anesthesia, or by hydrocortisone acetate. To determine whether ACTH releasing activity paralleled pressor activity in posterior pituitary extracts, Protopituitrin and various fractions from chromatograms of Pitressin have also been tested in rats with diabetes insipidus. Preliminary results indicate that pressor activity parallels ACTH releasing activity in this *in vivo* test system. The results are consistent with the hypothesis that ACTH release is controlled by the antidiuretic hormone of the neurohypophysis.

BOOK REVIEWS AND NOTICES

ATOMIC ENERGY RESEARCH AT HARWELL. By K. E. B. JAY. Pp. 144; 28 ills. New York: Philosophical Library, Inc., 1955. Price, $4.75.

THE purpose of this volume is to relate the story of the Atomic Energy Research Establishment at Harwell from the point at which it was left in the report of 1952 up to the formation of the United Kingdom Atomic Energy Authority in August, 1954. The material is presented in two major sections: Part I is primarily for nontechnical readers and includes advances in production, reactors, isotopes, electronic instruments, and special techniques; Part II is written for scientific readers and deals with fundamental research in the physics, chemistry and chemical engineering, and metallurgy divisions.

Persons interested in technical developments in the field of atomic energy will wish to read this report. C. Z.

THE BIOCHEMISTRY OF VITAMIN B_{12}. Edited by R. T. WILLIAMS. Pp. 123. New York: Cambridge University Press, 1955. Price, $3.75.

THE biochemistry of Vitamin B_{12} is thoroughly discussed in this report of the 13th Symposium of the Biochemical Society. Included are sections on the isolation and chemistry of Vitamin B_{12}, other factors related to this vitamin, and methods for its measurement. In addition there are chapters which deal with the absorption and excretion of Vitamin B_{12} in man, intrinsic factor, the function of Vitamn B_{12} in animal metabolism and in microörganisms.

Hematologists, nutritionists, biochemists, and workers in various fields of microbiology will find this a splendid review of current information regarding this important substance. C. Z.

UNTERSUCHUNGEN ZUR CHEMOTHERAPIE DER HAUTTUBERKULOSE. Verwertbarkeit kulturteller und tierexperimenteller Ergebnisse. By DR. MED. JOHANNES MEYER-ROHN. Universitäts-Hautklinik Hamburg-Eppendorf. Pp. 81; 12 ills. Stuttgart: Georg Thieme Verlag, 1956. (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $2.30.

THIS monograph contains a historical presentation of the chemotherapy of cutaneous tuberculosis, the experimental chemotherapy of tuberculosis of the skin (including *in vitro* study, animal experiments and experimental investigation with substances which are adaptable to the chemotherapy of cutaneous tuberculosis), clinical studies, discussion of results, conclusions and bibliography. Based on two years' work on 154 patients with cutaneous tuberculosis, the author found that isonicotinic acid hydrazide is well tolerated and an active therapeutic agent. In spite of the creditable presentation, this volume will have but little appeal to the American physician or even dermatologist, because of the small number of cases of tuberculosis of the skin in American practice. H. B.

THROMBOEMBOLIC DISEASE. By GEZA DE TAKATS, M.D., M.S., F.A.C.S., Division of Vascular Surgery, University of Illinois College of Medicine. Pp. 55. Springfield, Ill.: Charles C Thomas, 1955. Price, $2.25.

THIS small monograph, one of the American Lecture Series, is divided into three sections: 1) Clinical Forms of Thromboembolic Disease, 2) The Prevention of Thromboembolic Disease, and 3) Method of Treatment. The author has long been a student of this subject, and the value of the book lies in the fact that he writes of his personal experiences rather than summarizing the results of others. Emphasis is placed on the use of heparin, and the employment of prothrombin depressants is discouraged. There are other controversial issues on which he always takes a definite stand.

Although by no means comprehensive, this monograph should be of interest to all physicians. N. L.

TEXTBOOK OF MEDICAL PHYSIOLOGY. By ARTHUR C. GUYTON, M.D., University of Mississippi. Pp. 998; 577 ills. Philadelphia: W. B. Saunders Co., 1956. Price, $13.50.

THIS refreshingly new book is by an outstanding physiologist. It is entirely new and almost all the diagrams and figures are original and easy to comprehend. It is quite evident that the author appreciates the needs of medical students for whom this work can be recom-

mended. For them it has just the right amount of coverage and detail. At the same time it has avoided any suggestion of incompleteness. The parts which call on pathological physiology to illustrate the normal are well chosen.

M. O.

Systemic Lupus Erythematosus: Review of the Literature and Clinical Analysis of 138 Cases. By A. McGehee Harvey, M.D., Lawrence E. Shulman, M.D., Philip A. Tumulty, M.D., C. Lockard Conley, M.D., and Edyth H. Schoenrich, M.D. Pp. 437; 25 ills. Baltimore: Williams & Wilkins Co., 1955. Price, $3.00.

This is the best monograph yet written on the serious disorder, systemic lupus erythematosus. After a brief introduction and historical review, the authors consider in turn the pathology, etiology and pathogenesis, general aspects, clinical manifestations, and the hematologic manifestations of systemic lupus erythematosus. An excellent discussion of the L.E. cell phenomenon is followed by sections dealing with plasma protein abnormalities, and chronic biologic false positive serologic tests for syphilis. The chapters dealing with the clinical course, treatment, and prognosis are also especially well done. The authors are to be commended not only on their splendid treatment of the material based on their own extensive experience, but also for their careful and thorough review of the literature on systemic lupus erythematosus.

This monograph is unreservedly recommended to anyone interested in this serious disease which is of increasing importance.

C. Z.

Die Frühdiagnose des Uteruscarcinoms. By Prof. Dr. Med. Hans Limburg. 3rd ed. Pp. 334; 122 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $8.65.

This excellent book contains a comprehensive presentation and critical evaluation of the various methods, and of the results obtained by these methods, which are used in the early diagnosis of carcinoma of the uterus. Also, it contains a thorough discussion of cancer *in situ* of the cervix. On the basis of many years experience in this field the author recommends a combination of kolposcopy, cytology and biopsy. Of these methods, kolposcopy is found of particular value, though biopsy remains the most reliable method. Cytology is useful only in conjunction with kolposcopy and biopsy. Without these it is dangerous. Treatment for carcinoma should not be instituted without biopsy diagnosis. It is felt that this third edition of Limburg's book is indispensable for all engaged in the diagnosis of carcinoma of the uterus.

W. E.

Progress in Biophysics and Biophysical Chemistry. Vol. 6. Edited by J. A. V. Butler, University of London. Pp. 264; 108 ills. London: Pergamon Press, 1956. Price, $9.50.

This is the sixth in a series by outstanding authors. Physicists, physical chemists and biologists are included. This volume is of the same high quality as the others in the series. Chapters include Protamines and Nucleoprotamines, Structure of Chromosomes, Donnan Equilibrium, one on Transforming Principles, Neuromuscular Transmission, Models for Biological Excitation Processes, Sense Organs. All are well done and informative. Those on Transmission and Senses are outstanding.

M. O.

The Body Fluids. Basic Physiology and Practical Therapeutics. By J. Russell Elkinton, M.D., Associate Professor of Medicine, University of Pennsylvania, and T. S. Danowski, M.D., Renziehausen Professor of Research Medicine, University of Pittsburgh. Pp. 626; 172 ills. Baltimore: Williams & Wilkins Co., 1955. Price, $10.00.

These outstanding investigators have collaborated to bring to the medical profession a complete and clear picture of present-day knowledge of the body's fluid dynamics. The material is presented in four parts as follows: Basic Physiology, Basic Principles as Common Denominators in Clinical Situations, Disease Entities, and Clinical Dicta and Practical Therapeutics. There is also an Appendix which describes in detail the balance technique. Each chapter is well-written and well-illustrated, and concludes with a concise summary of its contents.

This book is unreservedly recommended to medical students, practicing physicians, and clinical investigators alike.

C. Z.

Introduction to Virology. By Gilbert Dalldorf, M.D. Pp. 102; 6 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $4.00.

This is a brief introductory book by Dr. Dalldorf who is the Director of Laboratories and Research of the New York State Depart

ment of Health. The book makes no claims to completeness though the major viral infections are adequately discussed. An excellent section considers the facilities needed in a virus laboratory and the more familiar laboratory procedures are considered in some detail. Though limited in scope the book will be of interest to those individuals who wish a brief, introductory text to the subject of virology. M. K.

Atlas der Kolpomikroskopie. By Prof. Dr. Tassilo Antoine and Priv. Doz. Dr. Viktor Grünberger. Pp. 224; 176 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $15.25.

This book deals with kolpomicroscopy, that is, the inspection of the surface of the portio with a microscope permitting 110 to 280 times magnification. The first 36 pages of the book contain a description in both German and English of the "incident-light microscope" and its usage. The subsequent pages show 80 to 90 photos of the surface of normal and disease portios and a similar number of photos of microscopic sections taken from the specimens. The illustrations are excellent. The legends are in German, English and Spanish. Of 571 patients with nonsuspicious erosions of the portio studied with this method, biopsies revealed carcinoma in 35 cases. Of these, 32 had been discovered previously with the kolpomicroscope. In some of these cases Papanicolaou's smear technique and Schiller's staining technique had been negative. The material presented in this book supports the contention of the authors that kolpomicroscopy is a valuable addition to our armamentarium in the diagnosis of cancer of the cervix. W. E.

Annual Review of Biochemistry, Vol. 24, 1955. Edited by J. Murray Luck, Hubert S. Loring and Gordon Mackinney. Pp. 805. Stanford, Calif.: Annual Reviews, Inc., 1955. Price, $7.00.

The editors and contributors to this treasured series have again produced a fine, readable volume after culling an enormous number of articles on each of the subjects reviewed. Included are reviews of Biological Oxidations; Nonoxidative and Nonproteolytic Enzymes; Proteolytic Enzymes; respectively, the Chemistry of Carbohydrates, of Phosphatides, of Proteins, Peptides, and Amino Acids, of Steroid Hormones, and of Antibiotics. The metabolism of lipids, carbohydrates, amino acids and proteins, and nucleic acids is dealt with in other chapters. Three sections are devoted to the water-soluble vitamins, and one each to fat-soluble vitamins, carotenoids, and the field of nutrition. Of special interest to clinicians is the chapter which deals with clinical applications of biochemistry. The current volume ends with the splendid review by Haddow on the Biochemistry of Cancer.

Biochemists, workers in other basic sciences, and clinicians interested in the more fundamental aspects of medicine will find this an invaluable reference book. C. Z.

The Hemorrhagic Disorders. By Mario Stefanini, M.D., Associate Professor of Medicine, Tufts University School of Medicine, and William Dameshek, M.D., Professor of Medicine, Tufts University School of Medicine. Pp. 368; 147 ills. New York: Grune & Stratton, Inc., 1955. Price, $11.75.

The authors, both widely known hematologists, have succeeded in their aim in writing this book, that is, to produce for the practicing physician a clinical and therapeutic approach to the various hemorrhagic states. Included are sections dealing with normal hemostasis; classification of hemorrhagic disorders; diseases due to defects of the vascular factor of hemostasis; thrombocytopenic states; diseases due to deficiency of factors participating in the blood coagulation mechanism; also those of complex etiology, involving multiple hemostatic factors; circulating anticoagulants; fibrinolysis; the bleeding tendency of obstetric accidents, and of dysproteinemias. These are followed by discussions of treatment, and of certain hereditary aspects of this group of conditions. Finally, there is an Appendix which is devoted to the methods for study of hemorrhagic disorders. The overall value of this volume in enhanced by numerous illustrations, a number of which are in color. C. Z.

Charter for the Aging. New York State Conference Convened by Governor Averell Harriman at the State Capitol in Albany, October, 1955. Pp. 659. Albany: New York State, 1956. May be obtained from the Office of Special Assistant, Problems of the Aging, Room 147, State Capitol, Albany, New York. Price, $3.00.

In October, 1955, there was held in Albany, New York, a Conference on Problems of the Aging convened by Governor Harriman. The present volume contains much of the material that was presented in the many special and general sessions. They cover most aspects of

the field of Gerontology including Community Organization, Education and Recreation, Employment, Group Care of the Aged; Health, Medical Care and Rehabilitation; Housing, Maintenance of Income and Prevention of Indigency, Mental Health, Retirement Policy and the Role of Religion. It is noteworthy that this significant contribution is based, in a large measure, on the splendid work over the years by the Joint Legislative Committee of the New York Assembly, under the able Committee Chairman, Senator Desmond.

R. K.

YEAR BOOK OF NEUROLOGY, PSYCHIATRY AND NEUROSURGERY, 1955–1956 SERIES. Edited by ROLAND P. MACKAY, M.D., Professor of Neurology, University of Illinois (Neurology), S. BERNARD WORTIS, M.D., Professor of Psychiatry and Neurology, New York University Bellevue Medical Center (Psychiatry), and PERCIVAL BAILEY, M.D., Professor of Neurology and Neurosurgery, University of Illinois, and OSCAR SUGAR, M.D., Associate Professor of Neurological Surgery, University of Illinois (Neurosurgery). Pp. 576; 97 ills. Chicago: The Year Book Publishers, Inc., 1956. Price, $7.00.

THIS year book maintains the standards of its predecessors. The articles are chosen well, the abstracts are concise yet informative and equally divided among the three specialties. The book is small enough for one's pocket, the type is easily read, and the illustrations are clear and to the point.

This book is eagerly awaited each year by those who have had the pleasure of reading it before. It is highly recommended to student, practitioner, or specialist, and to anyone interested in the progress of medicine. M. S.

ADVANCES IN PROTEIN CHEMISTRY VOL. X. 1955. Edited by M. L. ANSON, KENNETH BAILEY, AND JOHN T. EDSALL. Pp. 425; 105 ills. New York: Academic Press, Inc., 1955. Price, $9.00.

THIS volume continues the excellent series, and presents some facets of the wide interests of the protein chemist. Contributors are from England, Belgium and the United States.

The six monographs included present material covering the fine structure of several proteins: "The Nature of Phosphorus Linkages in Phosphoroproteins;" "Metabolism of the Aromatic Amino Acids;" and "Zinc and Metallo-enzymes" as well as data on intact whole proteins: "Hydrogen-ion Equilibria in Nature and Denatured Proteins" and "Fish Proteins."

One article is of widespread interest. "The Sea as a Potential Source of Protein Food" and carefully plays down the popular conception of the sea as a vast unused fish farm.

The articles are for the most part of interest to researchers in the particular field and are concluded in each case by an excellent bibliography. Under "Metabolism of Amino Acids" is included a short discussion of some metabolic anomalies of interest medically such as alkaptonuria, tyrosinosis, and oligophrenic phenylpyruvica; a brief outline of the genesis and metabolic fate of the thyroid hormones; and a short summary of serontonin (5-hydroxytryptamine) synthesis.

As usual, the publishers have presented an excellent publication in the details of binding and avoidance of obvious typographical errors. The authors and publishers are to be commended. J. B.

CLINICAL PATHOLOGY IN GENERAL PRACTICE. Specially Commissioned Articles from the British Medical Journal, October, 1953, to July, 1954. Pp. 321; illustrated. London: British Medical Association House, 1955. Price, 21 s.

THIS is a practitioner's handbook on Clinical Pathology, consisting of a collection of articles which originally appeared in the British Medical Journal in the Refresher Course series for General Practitioners. The material is divided into sections dealing with Practical Techniques, Renal and Alimentary Function, Infections, Haematology, Metabolic and Endocrine Disorders, and Special Problems. The latter is concerned with Skin Diseases, Tropical Diseases in Britain, and Industrial Poisoning. While some of the subject matter is pertinent primarily to medical practice in Britain, general practitioners everywhere will find this volume to contain much helpful information and guidance in its clinical interpretation. C. Z.

PREVENTIVE MEDICINE IN WORLD WAR II. ENVIRONMENTAL HYGIENE. Edited by COLONEL JOHN BOYD COATES, JR., MC, AND EBBE CURTIS HOFF, PH.D., M.D. Pp. 404; 25 ills. Washington: Office of the Surgeon General, Department of the Army, 1955. Price, $3.50.

THIS volume, the second in the Preventive Medicine Series of the History of the Medical

Department of the United States Army, is concerned with environmental hygiene and its impact upon the health, well-being, and morale of personnel during World War II. The authors include Tom F. Whayne, William A. Hardenbergh, Joseph J. Gilbert, Phillip T. Knies, Ralph R. Cleland, and the late James S. Simmons. All of these are men of special competence and extensive wartime experience. They are, therefore, highly qualified to sift the voluminous official documents for pertinent information. As a result of their efforts, a concise and accurate account of various aspects of Army environmental hygiene has been produced. Included are such topics as Food Management, Housing, Water Purification, Waste Disposal, Control of Insects, Rodent Control, Research Background of Insect and Rodent Control, Foreign Quarantine and Preventive Medicine in Ports of Embarkation and for Persons in Transit.

This volume is valuable as an historical document and for many sound principles upon which the management of future problems of environmental hygiene may be based.

C. Z.

ADVANCES IN VIRUS RESEARCH. VOL. III. Edited by KENNETH M. SMITH AND MAX A. LAUFFER. Pp. 338; illustrated. New York: Academic Press, Inc., 1955. Price, $8.00.

THIS is the third of an outstanding series of volumes which brings together critical review articles on representative viruses which cause diseases of man, of animals, of plants, and of bacteria. The present volume includes an excellent section on Comparative Biochemistry and Virology by Seymour S. Cohen; a fine review of The Chemotherapy of Viruses by R. E. F. Matthews and J. D. Smith; and an interesting survey of Tumor Viruses, by J. W. Beard, D. G. Sharp, and E. A. Eckert. In addition, there are interesting reviews of the Morphology and Development of Insect Viruses, by Kenneth M. Smith; the Multiplication of Plant Viruses in Insect Vectors, by K. Maramorosch; and the Current Status of Bacterial Transformations by Harriet Ephoussi-Taylor.

Workers concerned with the fundamental aspects of virus-plant and animal interrelationships will find much basic information in this valuable volume as well as in its predecessors.

C. Z.

LA PARTE FINALE DEL VENTRICULOGRAMMA (ONDA "U" E TRATTO "TU") E LA SINDROME DEI MUSCOLI PAPILLARI. BY DIOGENE FURBETTA, AMEDEO BUFALARI AND FRANCO SANTUCCI, University of Perugia. Pp. 280; 186 ills. Rome: Societa Editrice "Universo," 1955. Price, L. 3.500.

THE limited attention given to the U-wave in the past has induced the authors to investigate this component of the electrocardiogram. The book is divided into four sections which comprise ten chapters. Electrocardiograms, including esophageal leads, phonocardiograms, vectorial analysis, cardiograms pulse tracings and kymograms have been employed in the investigation. One chapter is dedicated to the characteristics of U-wave, T-U segment and their relation to the T-wave in normal conditions from the EKG and vectorial points of view. Five chapters are devoted to the effect of arrhythmias, myocardial pathology, vascular disturbances and also to the action of digitalis, quinidine and potassium. The last chapter deals with the papillary muscles. The lesions of the papillary muscles and their reflection on the U-wave and T-U segment constitute the syndrome of the papillary muscles. According to the authors, the U-wave is a protodiastolic wave normally positive and amplest at the zone of implantation of the papillary muscles of the left ventricle, not always positive in the septum and in the papillary muscles of the right ventricle, negative at the apex of the ventricles. The origin of U-wave seems to be principally in the papillary muscles. This wave represents the late repolarization of the papillary muscles due to their state of contraction during the protodiastole. The U-wave coincides with the closure of the semilunar valves, the isomeric phase of the diastole and the phase of rapid ventricular filling, and appears to bear a closer time relation to the aortic valves. The excitation wave invades the papillary muscles right after the activation of the septum and before sweeping the rest of the myocardium. However, the repolarization of the papillary muscles is later because their contraction persists during the isomeric phase of the diastole. Whenever a deviation of the terminal portion of the ventriculogram is present, a dysfunction of the papillary muscles should be considered. Increase in intraventricular pressure, coronary insufficiency, myocardial necrosis or degeneration, electrolyte disturbance are the etiological factors. In the left papillary syndrome the U-wave is inverted in Lead I, aVL and in the left precordial leads. It is upright in Lead III and the right precordial leads. The direction of the vector of U is from posterior to anterior and from left to right. Clinically, hypertension, anterior infarction or aortic valvular defects may be present. In the right

papillary syndrome the U-wave is inverted in Lead III, eventually in aVF, and in the right precordial leads. It is upright in Lead I and in the left precordial leads. The direction of the vector of U is to the left. Clinically, mitral stenosis, congenital diseases or right ventricular strain may be present. In the biventricular papillary syndrome (rare) the U-wave is inverted in all precordial leads and often in lead I and aVL. This may be found in hypertension, mitral stenosis and tricuspidal insufficiency. Most of the author's conclusions coincide with those expressed by authors in this country (The U wave of the Electrocardiogram. E. Lepeschkin: A.M.A. Arch. Int. Med., **196**, 600, 1955). As to the origin of the U-wave the authors offer a different explanation. They locate the origin of the last component of the EKG in the papillary muscles. Chapter I fully reviews the literature and a bibliography is appended to each chapter. The illustrations are clear, the paper is of good quality and the printing is neat. This book is of interest to cardiologists and cardiographers and may be a stimulant to research workers. F. P.

THE ROLE OF ALGAE AND PLANKTON IN MEDICINE. By MORTON SCHWIMMER, M.D., Clinical Assistant in Medicine, and DAVID SCHWIMMER, M.D., Assistant Professor of Medicine, New York Medical College, Metropolitan Medical Center. Pp. 85. New York: Grune & Stratton, Inc., 1955. Price, $3.75.

THIS interesting monograph summarizes such knowledge of algae and plankton as may be pertinent to medicine. Information concerning this important biologic area is not included in the usual curriculum of the physician. Accordingly, there is a brief section on definitions and classifications of algae and plankton which serves as an appropriate introduction to the field. This is followed by sections on nutritional and medicinal uses of seaweed (macroscopic algae) and of zooplankton and phytoplankton. Attention is drawn to some very interesting potential applications of phytoplankton. For example, it has been calculated that one kg. of fresh weight of *Chlorella* can easily supply the 25 L. of oxygen required by a 70 kg. man, as well as utilize the carbon dioxide exhaled by him. The use of algae in space ships and in atomic submarines is, therefore, an obvious consideration. Potential food supply is another area of potential importance for algae. The authors also touch upon a number of other interesting facets relating to algae, and include an extensive bibliography which lists 312 references. C. Z.

SURGICAL PHYSIOLOGY OF THE ADRENAL CORTEX. By JAMES D. HARDY, M.S. (CHEM.), M.D., Professor and Chairman, Department of Surgery, University of Mississippi. Pp. 191; 34 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $5.75.

THIS is a slim little volume concerned largely with the behavior of the adrenal glands in patients in various types of surgical stress. There is a rather sketchy review of adrenal physiology, normal and morbid, and the remainder of the 161 pages of text is concerned with the practical application of this rather basic knowledge. It is the reviewer's opinion that the general surgeon should not attempt his specialty without the knowledge contained in this book and should indeed go considerably further in his practice. For those lacking this information, this book will serve as a good starter. There is an admirable bibliography of 274 entries. E. A.

PATHOLOGY SEMINARS. Edited by ROBERT S. HAUKOHL, M.D., Marquette University School of Medicine, and W. A. D. ANDERSON, M.D., University of Miami School of Medicine. Pp. 195; 131 ills. St. Louis: C. V. Mosby Co., 1955. Price, $10.00.

THIS book consists of the recorded material from five pathology slide seminars, 1) on various tumors moderated by Lauren V. Ackerman, 2) on pathology of the skin moderated by Arthur C. Allen, 3) tumors of the nose and throat by Colonel J. E. Ash, 4) on various tumors by Arthur Purdy Stout and 5) various tumors by Rupert A. Willis.

Each case is prefaced by a short clinical summary, the consensus of diagnoses, the moderator's description and diagnosis and one or more plates illustrating the lesion.

The slide seminar is a proven teaching vehicle of considerable value dependent upon the moderator's choice of cases, knowledge and ability to transmit this knowledge to his audience and the opportunity of the pathologist to examine the slides through his own microscope. Of these, the last is the most important. In the "canned" seminar, all the flavor of the real affair is lost by the lack of this feature and black-and-white photomicrographs do little to replace it. Consequently a book of this sort is only an imitation of the real thing and a rather sterile and uninteresting one at that. E. A.

THE BEHAVIOR OF PULMONARY TUBERCULOUS LESIONS. By E. M. MEDLAR, Chief Pathologist, Division of Tuberculosis, New York State Department of Health. Pp. 244; 136 ills., many in color. New York: Hegeman Memorial Fund, Metropolitan Life Insurance Company, 1955.

DR. MEDLAR'S book appears at a time when tuberculosis sanitoriums are closing for lack of patients and phthisiologists are turning to lung cancer as the mainstay of their specialty. In one sense, this is a pity for this monograph on the pathology of pulmonary tuberculosis does much to dispel the myth and nonsense that has befogged the thinking and literature about this disease. Such statements as "It would appear that the interesting phenomenon of hypersensitivity to tuberculin is of relatively little significance" sound bold, even today. Had they been made by such an eminent authority 20 years ago, the course of the experimental work in this field might have been radically altered.

That Dr. Medlar is an authority is obvious in reading this text and its bibliography which contains 46 of the author's papers on this subject. For over 30 years, Dr. Medlar studied pulmonary tuberculosis by examining the tissue at the site of infection. He records what he has seen and bases his conclusions upon the facts rather than the literature. His materials and methods were available 50 years ago; the pity is that Dr. Medlar was not.

But, tuberculosis is not a disease of the past. It is still an important cause of mortality and morbidity. All physicians who assist in the diagnosis and management of the disease, and that means most of us, will find this book profitable reading. More important, it should be on the required reading list of all those who teach medical students in this subject.

E. A.

FIFTH ANNUAL REPORT ON STRESS, 1955–1956. Edited by HANS SELYE, M.D., Professor and Director, Institut de Medecine et de Chirurgie experimentales, Universite de Montreal and GUNNER HEUSER, M.D., Research Associate and Librarian of the Institut de Medecine et de Chirurgie experimentales, Universite de Montreal. Pp. 815. New York: MD Publications, Inc., 1956. Price, $20.00.

THESE "Annual Reports on Stress" are meant to act as supplements to the Monograph "Stress." In this 1955 Annual Report, 5 698 references have been classified and correlated.

The volume is divided into two main sections: 1) The General Physiology and Pathology of Stress and 2) The Special Physiology and Pathology of Stress. The first section consists of a discussion of the stress concept and the principal problems of stress research in 1955. There are also nine special articles written by guest authors, presenting their concepts of stress and related topics. In the second section, the data concerning the action of stress and the adaptive hormones upon various organs and metabolic activities are systematically listed.

These Annual Reports offer an excellent reference volume for those interested in obtaining specific data on various problems in the field of stress.

B. C.

NEW BOOKS

Composting: Sanitary Disposal and Reclamation of Organic Wastes. By HAROLD B. GOTAAS, Professor of Sanitary Engineering, Department of Engineering, University of California. Pp. 205; 49 ills. Geneva: World Health Organization, 1956. Price, $5.00.

A practical discussion of the problems of sanitary disposal and reclamation of organic wastes and methods for their solution in population groups ranging from a single farm to large cities.

R. K.

Supplement I, Atlas of Exfoliative Cytology. By G. N. PAPANICOLAOU, M.D., PH.D., Cornell Medical School. Pp. 42; 16 full page plates in color. Cambridge, Mass.: Harvard University Press for the Commonwealth Fund, 1956. Price, $4.00.

SUPPLEMENT I contains a number of colored plates in the exfoliative cytology of the female genital system, the respiratory system, the stomach and one on breast secretions. In reviewing the major text two years ago, this reader stated "the illustrations are so numerous and so similar that they lead to confusion rather than clear and definite concepts." The addition of more of the same would hardly seem to correct the situation.

E. A.

Understanding Human Behavior. By JAMES L. MCCARTNEY, M.D. Pp. 258; 12 ills. New York: Vantage Press, Inc., 1956. Price, $3.50.

HERE is a book for the layman that attempts to bring together what is known about human behavior and what can be done to help disturbed individuals gain a healthier state of mind. Written clearly and simply the book deals with man's anatomy, his nervous system, his mental makeup and his personality development. Beginning with the unborn child, it follows the process of growth from birth to maturity.

Behavior patterns are explained, the relationship of psychiatrist and patient explored, mental disorders are discussed and psychotherapy, including the new drugs, is explained. The author emphasizes the need for a better understanding of mental hygiene and presents the whole picture in frank and understandable terms.

O. E.

Personal Health Record. By Carl A. Dragstedt, M.D., Ph.D., Northwestern University Medical School. Pp. 64. Harrisburg, Pa.: The Military Service Publishing Company, 1956. Price, $1.00.

A laudable attempt toward the ideal of an individual's record of his own health. R. K.

The Practice of Psychosomatic Medicine as Illustrated in Allergy. By Hyman Miller, M.D., and Dorothy W. Baruch, Ph.D. Pp. 196. New York: Blakiston Division of McGraw-Hill Book Co., 1956. Price, $5.00.

The relationship of psychosomatic factors to allergic diseases is a controversial issue, especially among allergists. The present volume, written jointly by a husband-wife team, one an allergist and the other a psychologist, and representing enlargement of numerous papers in several journals, does nothing to resolve this issue. Thus, in the preface, the authors state that "allergic diseases are psychosomatic." How they explain seasonal hay fever on this basis is not made clear by the authors! They then consider in order modern (meaning psychosomatic) concepts in allergy, followed by etiologic and therapeutic approaches to diagnosis and treatment all slanted from the psychoanalytic viewpoint of the authors. No attempt is made to present in an impartial manner supportive evidence of other writers or controversial opinions. The volume is filled with dull repetitious recitals of detailed interviews with a few selected patients and contains an excess of psychoanalytic jargon, commonly found in similarly reported case studies.

While the practical value of the book is repeatedly stressed, the authors prove the opposite by ridiculous suggestions impossible of fulfillment in the average office or clinic; for example, to mention only one, that the doctor (or technician) first do a skin test on himself to prove to the child that it doesn't hurt. In reading through this volume, this reviewer could not escape the feeling that these authors were dealing with a specially selected group of allergy patients (including many pampered children who could have profited by the old-fashioned or "woodshed" brand of discipline) who already were problem cases regardless of their allergic disease; and that the two often were no more related etiologically than syphilis and tuberculosis affecting the same patient would be. While this volume might interest those with psychoanalytic leanings, it will be of no help whatsoever to anyone seeking information about the relationship between emotional upsets and allergic disease or how such problems should be managed. L. T.

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Dr. Richard A. Kern, Temple University School of Medicine, Philadelphia 40, Pa.

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References should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

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